2007

Bilateral occurrence of granulosa-theca cell tumors in an Arabian mare

Carlos M. Gradil, *University of Massachusetts - Amherst*
L. Frederico
M. Gerard
C. Pinto

Case Report Rapport de cas

Bilateral occurrence of granulosa-theca cell tumors in an Arabian mare

Lisa M. Frederico, Mathew P. Gerard, Carlos R.F. Pinto, Carlos M. Gradil

Abstract — An Arabian mare was referred for right granulosa-theca cell tumor (GTCT) evaluation. The mare was presented 4.5 years later for a left GTCT, after successfully conceiving and delivering a normal foal in the interim. The concurrent or nonconcurrent occurrence of bilateral GTCT in mares appears to be rare.

Résumé — Présence de tumeurs bilatérales de la granulosa et de la thèque chez une jument Arabe. Une jument Arabe a été référée pour l'évaluation d'une tumeur de la granulosa et de la thèque du côté droit (TGT). La jument avait été présentée 4,5 ans plus tôt pour une TGT du côté gauche, ayant entre temps conçu et mis au monde un poulain normal. La présence, simultanée ou non, de TGT bilatérales chez la jument semble être un fait rare.

(Traduit par Docteur André Blouin)

An 8-year-old, Arabian mare was presented to the North Carolina State University Veterinary Teaching Hospital (VTH) in 1999 for removal of an enlarged right ovary. The abnormal ovary was detected via transrectal ultrasonography while the mare was at a farm for breeding management. The mare had produced a live foal 3 y prior to presentation. The referring veterinarian had submitted serum for hormone analysis, which revealed elevated testosterone (681.5 pg/mL; reference range, 20 to 45 pg/mL) and inhibin (2.29 ng/mL; reference range, 0.1 to 0.7 ng/mL), and a decreased progesterone concentration consistent with absence of luteal tissue (0.4 ng/mL; reference range, ≤ 0.5 ng/mL). The owner reported that the mare had displayed unusually aggressive stallion-like behavior during the few months prior to presentation. Based on the hormone concentrations, ultrasonographic findings, and behavioral changes, a presumptive diagnosis of GTCT was made.

Case description

A presurgical transrectal ultrasonographic examination at the VTH revealed a moderately enlarged right ovary, approximately 9.7 cm in diameter, and a normal-sized, inactive left ovary. Multiple cysts were present in the periphery of the right ovary, including a larger cyst, measuring 6 cm in diameter, filled with a hypoechoic fluid. A right ovariectomy via a right ventral, diagonal paramedian approach was performed with the mare under general anesthesia.

Department of Clinical Sciences (Frederico, Gerard) and Department of Population Health and Pathobiology (Pinto, Gradil), College of Veterinary Medicine, North Carolina State University, 4700 Hillsborough Street, Raleigh, North Carolina 27606, USA.

Address all correspondence to: Dr. Gerard; e-mail: mat_gerard@ncsu.edu

Induction to anesthesia included xylazine (Sedazine; Fort Dodge Animal Health, Fort Dodge, Iowa, USA), 1.1 mg/kg bodyweight (BW), IV, diazepam (Diazepam injection, USP; Hospira, Lake Forest, Illinois, USA), 0.1 mg/kg BW, IV, and ketamine (Ketaset; Fort Dodge Animal Health), 2.2 mg/kg BW, IV. Butorphanol (Torbugesic; Fort Dodge Animal Health), 0.025 mg/kg BW, IV, was administered at the beginning of the surgical procedure. Anesthesia was maintained by 2% isoflurane (Attane; Minrad, Bethlehem, Pennsylvania, USA) delivered in 100% oxygen. Preoperatively, the mare received flunixin meglumine (Banamine; Schering-Plough Animal Health, Union, New Jersey, USA), 1.0 mg/kg BW, IV.

The ovarian pedicle was ligated by using size 2 synthetic absorbable suture and a stapling device (TA 90 stapling instrument; US Surgical Corporation, Norwalk, Connecticut, USA), and the ovary was removed from the peritoneal cavity. A routine 3-layer closure of the abdominal wall was performed. The ovary weighed 465 g, measured 11 cm × 8 cm × 7 cm, and contained multiple thick-walled cysts. Perioperatively, the mare received metronidazole (Metronidazole Tablets, USP; PLIVA, East Hanover, New Jersey, USA), 15 mg/kg BW, PO, q8h, potassium penicillin (Pfizerpen; Pfizer, New York, New York, USA), 22 000 IU/kg BW, IV, q6h, and gentamicin sulfate (Gentozen; Schering-Plough Animal Health), 4.4 mg/kg BW, IV, q24h, for 24 h. Postoperatively, phenylbutazone (Phenylzone Paste; Schering-Plough Animal Health), 2.2 mg/kg BW, PO, q12h for 4 d and then q24h for 5 d, was administered. Butorphanol, 0.05 mg/kg BW, IM, q8h, was administered for 2 d postoperatively. Decreased fecal output was noted on the day after surgery, at which time 1 gallon of mineral oil was administered via nasogastric tube and the feed intake was restricted to hand grazing thrice daily and bran mashes twice daily. The fecal output returned to normal and the mare was back on normal hay and grain rations by postoperative day 2. The incision was mildly edematous on day 2, but otherwise it was within normal limits and healed without complication.
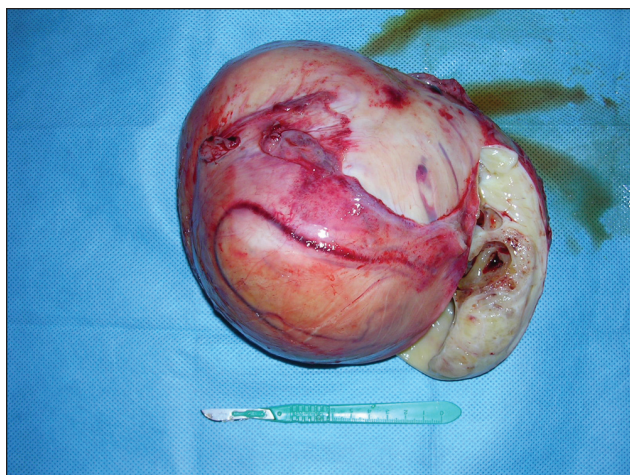
Figure 1. Left granulosa-theca cell tumor, after having been removed and partially incised.

Figure 2. Left granulosa-theca cell tumor, incised to reveal its large cystic center and multiple small cystic cavities in the wall of the tumor.

Histopathologic findings of the ovary were consistent with those of a GTCT and included closely packed, pleomorphic granulosa cells with indistinct cell borders and fibrillar eosinophilic cytoplasm. The neoplastic cells were arranged in cords and islands separated by a prominent fibrous stroma.

In 2004, the mare was presented to the VTH for evaluation of the remaining left ovary. Transrectal ultrasonography performed by the referring veterinarian had shown a hypoechoic mass on an enlarged ovary. The owner reported that the mare had been exhibiting stallion-like behavior, including mounting other mares in the pasture, for 5 mo prior to presentation. The mare had produced 1 foal since the right ovariectomy and had experienced no health problems other than mild weight loss, observed by the owner over a course of 3 mo. At the time of presentation to the VTH, the mare was in good body condition.

Palpation per rectum of the mare's reproductive tract and caudal part of the abdomen revealed a very large, smooth, slightly compressible mass, situated ventrally and slightly to the left of midline. Transrectal ultrasonography of the reproductive tract, as well as transabdominal ultrasonography through the left flank and ventral abdomen, showed a large mass at least 20 cm in diameter associated with the left ovary. Accurate measurement was difficult due to the size and position of the mass in the abdomen. Similarly to the tumor previously detected in the right ovary, the mass on the remaining left ovary had a large cystic center containing hypoechoic fluid, a few small eccentric and irregular cystic structures, and no evidence of normal ovarian parenchyma. A presumptive diagnosis of GTCT was made, and a left ovariectomy was recommended. Subsequent serum hormone analysis performed on blood drawn at presentation revealed a hormonal profile comparable with that of the previous presentation: elevated testosterone (270.7 pg/mL; reference range, 20 to 45 pg/mL) and inhibin (4.08 ng/mL; reference range, 0.1 to 0.7 ng/mL), and lowered progesterone (0.1 ng/mL; reference range, $\leq$ 0.5 ng/mL), indicating absence of active luteal tissue. Feed was withheld for 12 h before surgery. Preoperative medications consisted of potassium penicillin (Pfizerpen; Pfizer), 22 000 IU/kg BW, IV, gentamicin sulfate (Gentozen; Schering-Plough Animal Health), 4.4 mg/kg BW, IV,

and flunixin meglumine (Banamine; Schering-Plough Animal Health), 1.0 mg/kg BW, IV.

Anesthetic induction included xylazine (Sedazine; Fort Dodge Animal Health), 1.75 mg/kg BW, IV, butorphanol (Torbugesic; Fort Dodge Animal Health), 0.025 mg/kg BW, IV, midazolam (Midazolam Hydrochloride; Baxter Healthcare, Deerfield, Illinois, USA), 0.125 mg/kg BW, IV, and ketamine (Ketaset; Fort Dodge Animal Health), 2.2 mg/kg BW, IV. Anesthesia was maintained by 2% isoflurane (Attane; Minrad) delivered in 100% oxygen. Additional butorphanol, 0.025 mg/kg BW, IV, was administered approximately midway through the surgical procedure.

A 30-cm ventral midline incision was made extending craniad from the mammary glands. The ovarian pedicle was infiltrated with approximately 20 mL of 2% mepivacaine hydrochloride (Carbocaine-V; Pfizer) and then ligated by using size 2 synthetic absorbable suture and a stapling device (TA 90 stapling instrument). The pedicle was transected distal to the ligatures and the ovary was removed. The abdominal wall was closed by using a routine 3-layer technique.

The ovary weighed 2017 g and was approximately 25 cm in diameter with a large cystic center (Figures 1 and 2). Histopathologic findings of the left ovary were consistent with those of a GTCT, as evidenced by follicular arrangements of neoplastic granulosa cells separated by a moderate amount of well-differentiated mesenchymal stroma. Individual cells were columnar to irregular polyhedral and had small volumes of lightly basophilic to amphophilic cytoplasm. An IV butorphanol constant rate infusion (20 mg butorphanol per 5 L lactated Ringer's solution at 1L/h) was initiated immediately following recovery from anesthesia and continued for 48 h. The day after surgery, the mare displayed signs of moderate abdominal discomfort, manifested as standing in the far corner of the stall, pawing, and head-bobbing, and had a decreased appetite, decreased gastrointestinal motility, and decreased fecal output. Ranitidine (Ranitidine Tablets, USP; Apotex, Toronto, Ontario), 7 mg/kg BW, PO, q8h, was administered as prophylaxis against gastric ulceration. Additionally, one-half gallon of mineral oil was administered via nasogastric intubation. The incision site

was clean and dry with minimal swelling. On the 2nd post-operative day, the mare seemed more comfortable, was moving around the stall more, and was producing semiformed feces. By the 3rd postoperative day, the mare was bright and alert, passing normal amounts of soft stool, and had a normal appetite. The incision site remained dry and intact with mild edema. The mare received potassium penicillin (Pfizerpen; Pfizer), 22 000 IU/kg BW, IV, q6h, and gentamicin sulfate (Gentozen; Schering-Plough Animal Health), 4.4 mg/kg BW, IV, q24h for 5 d, as well as flunixin meglumine (Banamine; Schering-Plough Animal Health), 1.0 mg/kg BW, IV, q12h for 5 d, then every 24 h for 4 d. At the time of discharge from the VTH, the mare was comfortable, bright and alert, with a normal appetite, and passing normal amounts of formed feces. The incision site was clean and dry with no swelling. Follow-up conversations with the owner 3 mo and 6 mo after surgery indicated that the incision had healed without complication. The owner also reported that the mare was doing very well and no longer displayed stallion-like behavior.

Discussion

Granulosa-theca cell tumor is the most common ovarian neoplasm found in the mare and the most frequent indication for nonelective ovariectomy (1). Additional differential diagnoses for ovarian enlargement in the mare include hematoma, abscessation, teratoma, cyst adenoma, large anovulatory follicles, and formation of supplementary corpora lutea in the ovaries of pregnant mares, especially during days 40 to 70 of gestation. Mares affected with GTCT often exhibit irregular estrous cycles characterized by either anestrus or nymphomania; stallion-like behavior or aggressiveness toward other horses is common. Transrectal palpation and ultrasonography reveal an abnormally enlarged ovary accompanied by an inactive, small contralateral ovary. The ovarian fossa is invaded by tumoral tissue during the early stages of the tumor and is not readily palpable per rectum, although the occurrence of GTCT in a mare with a normal ovarian fossa has been reported (2). Ultrasonographic examination of GTCT typically shows the presence of multiple cystic compartments, resulting in the so-called honey-comb appearance. Occasionally, a single large central cyst containing hypoechoic fluid is observed, as in the mare described in this report. Examination of the contralateral ovary by transrectal ultrasonography reveals the absence of follicular activity and luteal tissue. Cases of concurrent or nonconcurrent bilateral ovarian GTCT have rarely been reported in the mare, and the current literature is limited to brief descriptions of bilateral cases (3,4). Several reports exist for unilateral cases, and surgical removal, using various techniques, has been well documented (5–15). This report describes a mare that reproduced successfully between bilateral GTCTs that developed a number of years apart.

Surgical removal of GTCT is the treatment of choice for this condition (1,5–9). Two different surgical approaches were used to access and remove the tumors in this horse. The ventral diagonal paramedian approach is well tolerated with up to 50% of mares reported to experience only mild postoperative discomfort (7,9). Tumors up to 25 cm in diameter have been

removed via this approach and it is suggested that tumor size is not a limitation in choosing the diagonal paramedian incision (7). The caudoventral midline approach was chosen due to the tumor's size and its position within the abdomen. The degree and duration of postoperative discomfort manifested after the 2nd ovariectomy was likely due to the differences in tumor size, which affected the length and location of the abdominal incision. In addition, larger tumors tend to have a thickened, shorter pedicle that requires more manipulation for successful ligation and removal (7). The caudoventral midline approach provides adequate exposure and access to the ovarian pedicle (10). If a surgeon feels that the size of the ovary precludes easy exteriorization through a diagonal paramedian incision, the midline approach should always be considered.

Granulosa-theca cell tumors are usually benign; however, metastatic disease in the mare with them has been described (11,12). The 2nd GTCT in this mare was unlikely due to metastasis. A reproductive examination performed 1 y following the first ovariectomy (right ovary) had revealed no abnormalities on the remaining left ovary. In addition, there was no gross evidence of other abdominal organs or lymph nodes being affected at the time of the 2nd surgery and the mare had no clinical signs of systemic illness. However, it is possible that a developing tumor was not identified early in its growth and that the mare was able to conceive and foal in its presence.

In addition to rare cases of malignancy, other complications secondary to GTCT include small colon obstruction, adhesions, ovarian torsion, and hemoperitoneum (1,10,13,15). The possibility of these complications justifies the removal of these tumors; however, they are generally excised due to their progressive growth and abnormal ovarian function, with consequent behavioral changes in the affected mare.

Granulosa-theca cell tumors may produce different combinations of testosterone, inhibin, and estrogen (16–18). Behavioral changes in affected mares vary from stallion-like to nymphomania, and even anestrus. These patterns of behavior may be associated with the predominant hormone secreted by the tumor (18). The mare in this report displayed the same behavioral changes with each GTCT and the hormonal profiles during both occasions were clinically similar. Excessive circulating testosterone concentration is usually responsible for the onset of aggressive behavior (18) and occurs in approximately 50% of mares diagnosed with GTCT (14,16,19). The elevated serum inhibin concentration was not unexpected. Eighty-seven percent of mares with GTCT have increased circulating inhibin concentration (14,16,17,19). Although serum estrogen concentrations were not available for either tumor episode in this case, excessive production of estrogen was not likely, as neither nymphomania nor prolonged estrus occurred. In cases of concurrent or nonconcurrent bilateral GTCT in mares, it is not known if both tumors always produce the same type of hormones.

Excessive hormone production by a GTCT also affects the reproductive capability of a mare due to an inhibitory influence on the unaffected ovary. Usually the unaffected ovary has a normal or smaller than expected diameter and is inactive (17,18), as in this case. High inhibin concentrations produced by the neoplastic granulosa cells may inhibit follicle-stimulating hormone

(FSH) by negative feedback on the pituitary gland (14). This inhibitory effect on FSH release results in a quiescent ovary. Once the affected ovary is removed, the inactive contralateral ovary may return to normal function 30 d to 14 mo following surgery; the time of the year seems to influence the time taken to return to normal ovarian function, as many mares will resume cyclicity during the following breeding season (20). In the present case, the mare's owner observed estrus-like behavior 12 mo following the 1st ovariectomy, and by palpation per rectum and transrectal ultrasonography did not detect any abnormality in size or function of the left ovary; she was bred and produced a foal in the following year. It is unclear whether mares with a history of GTCT of 1 ovary are at higher risk than other mares for development of a second GTCT. However, owners should be made aware of the possibility of bilateral occurrence, especially in cases where the mare is intended for use as breeding stock.

CVJ

References

1. Trotter G, Embertson R. The uterus and ovaries. In: Auer JA, Stick JA, eds. Equine Surgery. 2nd ed. Philadelphia: WB Saunders, 1999:575–583.
2. Hinrichs K, Cochran SL, Schelling SH, Steckel RR. Granulosa-theca cell tumor associated with an ovulation fossa and normal ovarian stroma in a mare. J Am Vet Med Assoc 1992;200:696–698.
3. Turner TA, Manno M. Bilateral granulosa cell tumor in a mare. J Am Vet Med Assoc 1983;182:713–714.
4. McCoy DJ. Diabetes mellitus associated with bilateral granulosa cell tumors in a mare. J Am Vet Med Assoc 1986;188:733–735.
5. Ragle CA, Southwood LL, Hopper SA, Buote PL. Laparoscopic ovariectomy in two horses with granulosa cell tumors. J Am Vet Med Assoc 1996;209:1121–1124.
6. Rodgerson DH, Brown MP, Watt BC, Keoughan CG, Hanrath M. Hand-assisted laparoscopic technique for removal of ovarian tumors in standing mares. J Am Vet Med Assoc 2002;220:1503–1507.
7. Carson-Dunkerley SA, Hanson RR. Ovariectomy of granulosa cell tumors in mares by use of the diagonal paramedian approach: 12 cases (1989–1995). J Am Vet Med Assoc 1997;211:204–206.
8. Fessler JF, Brobst DF. Granulosa cell tumor. Cornell Vet 1972;62:110–123.
9. Moll HD, Slone DE, Juzwiak JS, Garrett PD. Diagonal paramedian approach for removal of ovarian tumors in the mare. Vet Surg 1987;16:456–458.
10. Sedrish SA, McClure JR, Pinto C, Oliver J, Burba DJ. Ovarian torsion associated with granulosa-theca cell tumor in a mare. J Am Vet Med Assoc 1997;211:1152–1154.
11. Patrick DJ, Kiupel M, Gerber V, Carr EA. Malignant granulosa-theca cell tumor in a two-year-old miniature horse. J Vet Diag Invest 2003;15:60–63.
12. Gift LJ, Gaughan EM, Schoning P. Metastatic granulosa cell tumor in a mare. J Am Vet Med Assoc 1992;200:1525–1526.
13. Rambags BP, Stout TA, Rijkenhuizen AB. Ovarian granulosa cell tumours adherent to other abdominal organs; surgical removal from 2 warmblood mares. Equine Vet J 2003;35:627–632.
14. Chopin JB, Chopin LK, Knott LM, Kretser DM, Dowsett KF. Unusual ovarian activity in a mare preceding the development of an ovarian granulosa cell tumour. Aust Vet J 2002;80:32–36.
15. Wilson DA, Foreman JH, Boero MJ, Didier PJ, Lerner DJ. Small colon rupture attributable to granulosa cell tumor in a mare. J Am Vet Med Assoc 1989;194:681–682.
16. Christman SA, Bailey MT, Wheaton JE, Troedsson MHT, Ababneh MM, Santschi EM. Dimeric inhibin concentrations in mares with granulosa-theca cell tumors. Am J Vet Res 1999;60:1407–1410.
17. Bailey MT, Troedsson MH, Wheaton JE. Inhibin concentrations in mares with granulosa cell tumors. Theriogenology 2002;57:1885–1895.
18. Watson ED. Reproduction. In: Mair T, Love S, Schumacher J, Watson E, eds. Equine Medicine, Surgery and Reproduction. London: WB Saunders, 1998:278–309.
19. McCue PM. Equine granulosa cell tumors. Proc 38th Annu Conv Am Assoc Equine Pract 1992:587–593.
20. Clark T. Clinical management of equine ovarian neoplasms. J Reprod Fertil Suppl 1975;23:331–334.