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Case Report

Luteoma in two mares treated by ovariectomy

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Summary

A 15-year-old Paint mare (Case 1) and a 15-year-old Arabian mare (Case 2) were presented for aggressive and undesired behaviour. Reproductive evaluation revealed, initially, an enlarged ovary with a smaller/normal sized contralateral ovary in each case. Granulosa cell tumour (GCT) panel testing revealed elevated inhibin B in both cases and elevated anti-Mullerian hormone (AMH) levels only in Case 1 determined from currently established reference ranges. Based on a presumptive diagnosis of GCT, bilateral standing ovariectomy was elected for both mares. In each case neoplastic tissue consistent with luteoma was detected only on histological examination in the smaller/normal sized left ovary; the right ovary appearing normal. Long-term follow-up was performed 1 year and 5 years post-operatively by telephone. The owners were satisfied with the outcome and each patient demonstrated resolution of aggressive stallion-like behaviour. Each case returned to the owners' intended use. In conclusion, luteoma should be considered as a differential diagnosis for ovarian neoplasms in horses related to behavioural abnormalities, even in normal-sized ovaries.

Introduction

Luteomas are a rare type of mammalian ovarian sex cord tumour derived from or resembling ovarian endocrine tissues. Ovarian sex cord tumours can be hormonally active with a myriad assortment of histological appearances making differentiation complicated (Agnew & MacLachlan, 2017). Ovarian sex cord tumours (gonadostromal tumours) can be further classified into granulosa cell tumours (GCT), granulosa theca cell tumours, luteomas, thecoma, Sertoli cell tumour of the ovary, Leydig cell tumour, androblastoma, arrhenoblastoma, interstitial gland tumour and lipid cell tumour of the ovary (Agnew & MacLachlan, 2017). Luteomas may also be classified as lipid cell or Leydig-like tumours (Agnew & MacLachlan, 2017). Luteomas were first reported in humans in 1963 (Sternberg, 1963) and surgical intervention is unnecessary unless ovarian torsion or obstructive labour arises (Wang et al., 2005). Luteomas have been reported in veterinary species including cows, dogs, cats (Nielsen & Misdorp, 1976; Gelberg & McEntee, 1985; MacLachlan, 1987; Patnaik & Greenlee, 1987), and dolphins (Nishina et al., 2017). To date only a single equine luteoma was described in a recent retrospective case series (Renaudin et al., 2020).

In mares, commonly reported ovarian neoplasia includes GCT, teratomas, serous cystadenomas and adenocarcinomas; GCT accounting for 85% of equine ovarian tumours (Bosu et al., 1982; McCue et al., 2006). GCT are also sex cord tumours capable of expressing sex hormones and altering equine behaviour (McCue et al., 2006). Diagnostic investigations include transrectal palpation, ultrasound and hormonal assays (McCue et al., 2006; Claes & Ball, 2016). However, definitive diagnosis is ascertained only with histopathology (McCue et al., 2006). A GCT panel (Clinical Endocrinology Laboratory, University of California-Davis) that measures testosterone, inhibin B and anti-Mullerian hormone (AMH) is frequently submitted for mares with aggressive stallion-like behaviour and enhances a presumptive diagnosis of GCT (Conley & Ball, 2018 ; McCue et al., 2006). Histological examination alone is able to differentiate between a luteoma or GCT as a GCT hormonal panel may show elevated hormonal levels for either sex cord tumour type. The objective of this paper is to report the clinical findings, diagnostic results and long-term follow-up for two mares with a diagnosis of luteoma following bilateral ovariectomy.

Case presentations

Case 1

History, clinical findings and diagnosis

A 15-year-old Paint mare was referred to Iowa State University, Lloyd Veterinary Medical Centre during the summer of 2019 by Iowa State University Equine Field Services, for laparoscopic ovariectomy. Referral information reported aggressive behaviour and a GCT endocrine panel (Clinical Endocrinology Laboratory; UC Davis) submission 2 months prior to presentation (**Table 1**). The latter demonstrated elevated inhibin B (0.22 ng/ml, normal range 0.002–0.1 ng/ml) and AMH concentrations (7.3 ng/ml, normal range 0.1–6.9 ng/ml) for a cycling mare while testosterone concentration (0.0435 ng/ml, normal range 0.02–0.045 ng/ml) was normal based on established reference ranges (Uliani et al., 2019). Transrectal palpation revealed a small left ovary and slightly larger right ovary. Transrectal ultrasound showed multiple

TABLE 1: Testosterone, inhibin and anti-Mullerian hormone (AMH) values reported for each case with currently established reference ranges (Clinical Endocrinology Laboratory, UC Davis)

	Testosterone (ng/ml)	Inhibin (ng/ml)	Anti-Mullerian hormone (ng/ml)
Reference range	0.02–0.045	0.002–0.1	0.1–6.9
Case 1	0.045	0.22†	7.3†
Case 2	0.032	0.38†	4.4

† Denotes elevated value.

small follicles (diameter <15 mm) on the left ovary. The right ovary had a circular area (diameter ~30 mm) with a hyperechoic rim and hypoechoic centre containing hyperechoic strands (**Fig 1**). Presumptive differential diagnoses included GCT or haemorrhagic anovulatory follicle of the right ovary. The owner reported no breeding expectations. The mare was started on a pelleted diet regimen following initial evaluation.

On presentation to Iowa State University, Lloyd Veterinary Medical Centre, the mare was in good body condition with vital parameters within normal limits. Ultrasound showed the right ovary had regressed with multiple small follicles present with no evidence of the previously suspected GCT or haemorrhagic anovulatory follicle present.

Treatment

The day following presentation, a 14-g short-stay i.v. catheter (Mila International Inc.) was placed with the mare receiving perioperative gentamicin (Gentamicin Sulphate Solution, MWI Animal Health; 6.6 mg/kg i.v.), procaine penicillin G (PenOne Pro, Norbrook Laboratories Limited; 22,000 IU/kg i.m.) and flunixin meglumine (Prevail, MWI Animal Health; 1.1 mg/kg i.v.). There was history of tetanus toxoid vaccine administered that spring. A detomidine hydrochloride (Dormosedan, Orion Corporation; 0.008 mg/kg i.v.) and butorphanol (Torbugesic, Zoetis US; 0.02 mg/kg i.v.) bolus was administered followed by continuous rate infusion (CRI) of detomidine hydrochloride (Dormosedan, Orion Corporation; 0.04 mg/kg/h i.v.) regulated as needed. Standing laparoscopic bilateral ovariectomy was performed as described (Woodie, 2019). All incisions were coated with aluminium-based aerosol spray (Aluspray, Neogen Corporation) as a protective barrier following portal closure.

Pathology

Gross findings. Both ovaries appeared normal on external inspection, and were placed in 10% neutral buffered formalin (NBF) and submitted for histopathological examination; they were sectioned at 0.5-cm intervals. The right ovary appeared within normal limits with scattered small (1–3 mm in diameter) cystic structures (developing follicles). The left ovary contained a central, 7 mm in diameter cystic structure (developing follicle) and a discrete, dark red mass approximately 8 mm in diameter. Four sections of each ovary were trimmed and processed routinely to paraffin wax. Deparaffinised sections (thickness 4 um) were rehydrated through graded alcohols and stained with haematoxylin and eosin (HE).

Histological findings. On histopathological examination, the dark red mass consisted of a uniform population of large polyhedral cells with abundant, finely vacuolated to granular eosinophilic cytoplasm. Many cells contained numerous small, well-demarcated, clear cytoplasmic vacuoles (**Fig 2**). Polyhedral cells had moderately sized, round to slightly oval nuclei with finely stippled chromatin and one to three large nucleoli. Anisokaryosis was mild and mitotic figures were rare. Polyhedral cells were arranged in small clusters and cords separated and surrounded by abundant haemorrhage. These findings were considered to be consistent with a diagnosis of luteoma.

Case progression

Week 1 post-operative. The mare remained comfortable with parenteral antibiotics and nonsteroidal anti-inflammatories continued for 3 days post-operatively. The mare remained hospitalised for 6 weeks post-operatively per owner request.

Week 4 post-operative. The mare developed soreness and swelling at the larger left flank incision. Ultrasonography showed subcutaneous oedema with no other significant findings. Diclofenac 1% sodium (Surpass, Boehringer Ingelheim Vetmedica) and cold compresses were applied twice daily. The next day, purulent discharge was present along the area of incisional oedema. Sutures were removed and sulphadiazine/trimethoprim (Uniprim, Neogen Corporation; 75 mg/kg per os b.i.d.) was administered for 10 days. Culture and sensitivity of the incision reported *Staphylococcus aureus* and *Enterobacter cloacae* growth, both susceptible to sulphadiazine/trimethoprim. Loose faeces were observed 10 days later and antibiotics were discontinued. The loose faeces resolved spontaneously within 48 h. The incision sites healed adequately with no further discharge, and the mare was discharged.

Outcome

One year post-operatively, the owner was contacted and reported the aggressive behaviour had resolved.

Case 2

History, clinical findings and diagnosis

A 15-year-old Arabian maiden mare was presented at Aspen Creek Veterinary Hospital in 2015 for lameness evaluation and a 2-year history of aggressive behaviour. The mare reportedly charged and injured the owner several times with other behaviour including biting, mounting other horses and vocalising when mares were present or displayed signs of oestrus. The mare was in good bodily condition with normal clinical parameters and displayed the behaviour described by the owner. There were no signs of oestrus or vaginal discharge. A GCT endocrine panel (Clinical Endocrinology Laboratory, UC Davis) showed a marginally elevated AMH concentration (4.4 ng/ml, normal range 0.1–3.8 ng/ml) with normal levels of inhibin (0.38 ng/ml, normal range 0.1–0.7 ng/ml) and testosterone (0.032 ng/ml, normal range 0.02–0.045 ng/ml). However, GCT panel reference ranges were updated for inhibin B and AMH after Case 2 (Uliani et al., 2019). **Table 1** shows the reported panel levels for Case 2 compared to Uliani et al. (2019) ranges. Thus, in retrospect, the AMH level was normal, with a raised inhibin level. Transrectal ultrasonography revealed a slightly subjectively enlarged right ovary and normal sized left ovary (no measurements recorded for either ovary). A presumptive

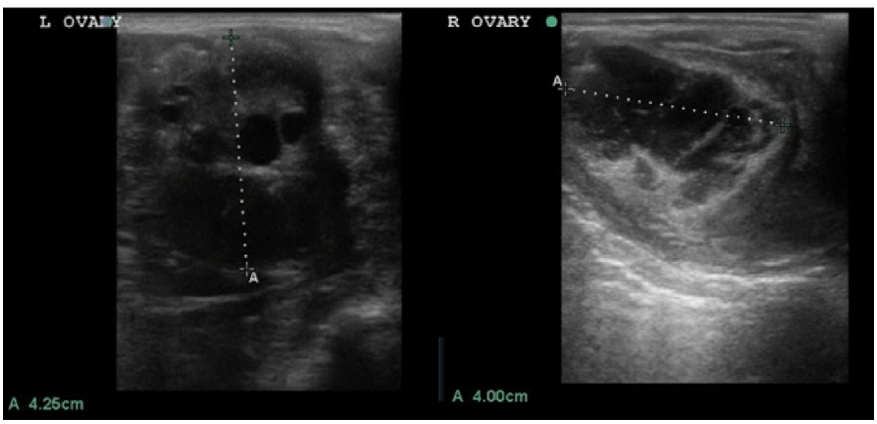

Fig 1: Case 1 transrectal ultrasonography of the right and left ovary. Transrectal ultrasound showed multiple small follicles (diameter <15 mm) on the left ovary. The right ovary had a circular area (diameter ~30 mm) with a hyperechoic rim and mostly hypoechoic centre containing hyperechoic strands.

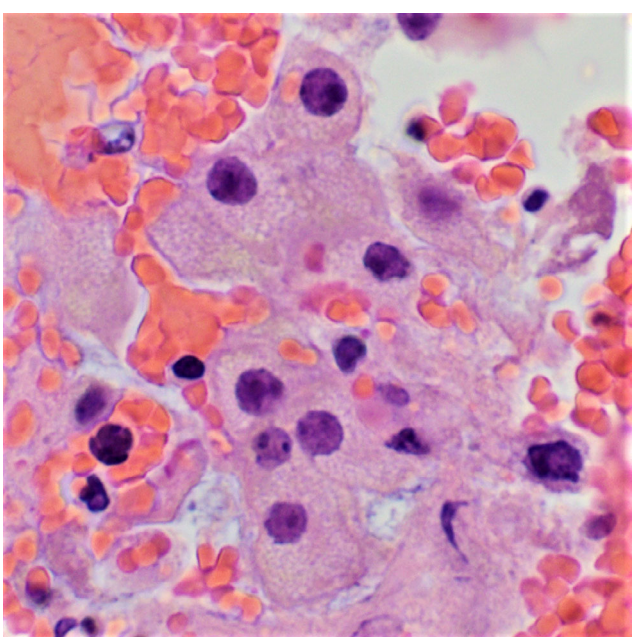

Fig 2: Case 1 ovarian histopathology: the neoplasm consists of clusters of polyhedral cells with abundant finely vacuolated eosinophilic cytoplasm separated and surrounded by abundant haemorrhage. H&E (60×).

diagnosis of GCT was made. The owner expressed no preparation for breeding and opted for an elective, bilateral ovariectomy. A pelleted diet regimen was initiated.

Surgical ovariectomy

A 14-g short-stay i.v. catheter (Mila International Inc.) was placed and the mare received perioperative gentamicin (Gentamicin Sulphate Solution, MWI Animal Health; 6.6 mg/kg i.v.), procaine penicillin G (PenOne Pro, Norbrook Laboratories Limited; 22,000 IU/kg i.m.) and flunixin meglumine (Prevail, MWI Animal Health; 1.1 mg/kg i.v.). There was history of tetanus toxoid vaccine administered within the year. Detomidine hydrochloride (Dormosedan, Orion Corporation; 0.008 mg/kg i.v.) and butorphanol (Torbugesic, Zoetis US; 0.02 mg/kg i.v.) boluses were given followed by detomidine hydrochloride (Dormosedan, Orion Corporation; 0.04 mg/kg/h i.v.). CRI was adjusted as needed for restraint. Standing flank laparotomy bilateral ovariectomy was performed (LeBlanc, 1999).

Pathology

Both ovaries were placed in 10% NBF and submitted for histopathological examination, but the appearance was not recorded. Following fixation, the tissues were processed routinely to paraffin wax, representative sections from both ovaries were cut at 4 μm and stained with HE. Histological examination revealed normal ovarian tissue with a fibroblastic connective tissue stroma with scattered haemosiderosis. Multiple, variably sized follicles (2–16 mm) in different stages of development, sometimes vesicular, were present. In the left ovary, a focal mass composed of sheets, aggregates and cords of oval, cuboidal, elongate to polyhedral cells with abundant eosinophilic, slightly vacuolated cytoplasm and round to oval nuclei containing a granular chromatin pattern and prominent single nucleolus was seen. Occasional mitoses were observed. The mass had irregular margins and compressed adjacent ovarian tissue. These findings were considered to be consistent with a diagnosis of luteoma.

Case progression

The mare remained comfortable after surgery. Parenteral antibiotics and nonsteroidal anti-inflammatories were continued for 3 days post-operatively. The mare was discharged from the hospital the day after discontinuing antibiotics. No surgical complications were noted following hospital discharge.

Outcome

When contacted 5 years post-operatively, the owner reported following ovariectomy the aggressive behaviour had resolved with the mare performing as intended for pleasure riding.

Discussion

In this report, luteoma was the histopathological diagnosis in the normal-sized left ovary of two horses, associated with

variably elevated levels of inhibin B and anti-Mullerian hormone. Equine luteoma may be a cause of aggressive stallion-like behaviour with altered GCT panel results in mares which resolves after bilateral ovariectomy. Both cases described in this report presented with aggressive and unwanted behaviour towards other horses, a frequent complaint connected with GCT in horses (McCue et al., 2006). Long-term follow-up revealed resolution of aggressive behaviour after ovariectomy of the luteoma affected ovary in each case, which is akin to GCT ovariectomy (McCue et al., 2006) and the only other report of equine luteoma (Renaudin et al., 2020). These findings suggest removal of a luteoma by ovariectomy may achieve ovariectomised mare behaviour. Further studies are necessary to determine if luteoma removal via unilateral ovariectomy will achieve normal behaviour.

Equine ovarian neoplasms may present comparably in behaviour, transrectal palpation and ultrasonography (Renaudin et al., 2020). Evaluation of the ovaries described in this case report indicated that one ovary was slightly larger than the contralateral ovary, a frequent finding in GCT cases, although normal sized/bilateral GCT cases have been reported (McCue et al., 2006; Renaudin et al., 2020). In the present cases both tumours were identified in a normal sized ovary, similar to that described by Renaudin et al. (2020). The fact that the normal sized ovary contained the luteoma suggests submitting both ovaries for histopathology after bilateral ovariectomy may be essential for diagnosis. In cases where only one enlarged ovary is removed and aggressive stallion-like behaviour continues, a luteoma in the remaining ovary should be considered.

Classification of sex cord stroma tumours is based on the resemblance of the predominant cell population to normal constituents of the ovary. The histological features of this tumour were most consistent with a luteoma as cells most closely resembled those of the corpus luteum, consisting of clusters and cords of polyhedral cells with abundant finely vacuolated to granular eosinophilic cytoplasm. There was no evidence of a supporting spindle cell population, disorganised attempts at follicle formation or Call–Exner bodies suggestive of a granulosa cell tumour, and the neoplastic population was not composed of spindle-shaped cells containing cytoplasmic lipid vacuoles, as would be expected with a thecoma (Agnew & MacLachlan, 2017).

Luteoma displays the ability to alter inhibin B and AMH (Conley & Ball 2018; McCue et al., 2006). Recently, Uliani et al. (2019), reported updated reference ranges for the hormones measured in a GCT panel. In Case 1, GCT panel testing revealed elevated inhibin B and anti-Mullerian hormone (AMH) levels based on recently established reference ranges (Uliani et al., 2019). In Case 2, inhibin levels (0.38 ng/ml) were within normal range at the time of submission but were elevated compared to revised reference ranges (Uliani et al., 2019). At the time of submission, the AMH level was raised but would now be considered normal (Uliani et al., 2019). In the single case of luteoma reported by Renaudin et al. (2020), normal levels were observed for inhibin, AMH and testosterone. This suggests that luteoma may have varying GCT hormone panel results making diagnosis prior to histopathological examination challenging. In both cases reported here, testosterone levels were normal. Further work is needed to determine if luteoma may affect testosterone levels. Thus, luteoma may present with or without abnormal GCT panel results. In cases where ovariectomy is not elected by the owner, in an attempt to alleviate clinical signs, the authors recommend a repeat reproductive evaluation with imaging and hormonal assays to determine if there are any more appreciable abnormalities on evaluation. These cases may highlight the possibility of neoplasms affecting behaviour that are initially difficult to detect with routine methods of evaluation.

Long-term follow-up performed 1 year and 5 years post-operatively revealed resolution of aggressive and stallion sexual-like behaviour as reported by the owners. Thus, with other, identified sex cord tumours, ovariectomy may carry a similar prognosis (McCue et al., 2006). That luteoma was identified only on histological examination in the normal, left ovaries suggests that ovariectomy may be considered even when the ovary size is subjectively normal. Although there is less research documenting luteoma, in human medicine, luteomas have been removed without signs of metastasis (Wang et al., 2005). Future studies that include complete necropsy would be necessary to determine if luteomas have metastatic potential in horses.

Conclusion

In conclusion, equine luteoma can cause unwanted behaviour and be diagnostically challenging but has a good prognosis following bilateral ovariectomy. It may be underdiagnosed if both ovaries are not submitted for histopathology.

Authors' declarations of interest

No conflicts of interest have been declared.

Ethical animal research

The owners of all patients have given their approval of using information from records including picture.

Authorship

E. Combs acquired the information from each individual case information, revised multiple drafts with conceptualisation and interpretation of all information. T. Beachler interpreted information regarding theriogenology and endocrine testing, revised multiple drafts with conceptualisation and interpretation of all information. J. Troy acquired the information from each individual case information, revised multiple drafts with conceptualisation and interpretation of all information. A. Olds-Sanchez was involved with Case 2 and provided all information for that case, and revised multiple drafts with co-authors. J. Howard was involved with Case 1 and referred it to Iowa State University and revised multiple drafts with co-authors. A. Fales-Williams is the pathologist who rendered interpretation for Case 1 histopathology and revised drafts with co-authors, especially for histopathology. M. Yaeger is a pathologist who assisted with interpretation of Case 1 histopathology and draft revisions to better clinically interpret the findings. D. Tatarniuk was involved with Case 1 and performed the surgery, and brought information of both cases from A. Olds-Sanchez and Case 1, and revised drafts with co-authors. All authors approved the final version.

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