

Concurrent occurrence of granulosa cell tumor, uterine adenomyosis, cystic endometrial hyperplasia and uterine serosal inclusion cyst in a bitch

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Abstract

An eleven-year-old Doberman-German Shepherd mixed bitch was presented with vulvar enlargement, vaginal discharge, and bleeding for two months and a week before, respectively. The dog was operated for routine ovariohysterectomy. During the surgery, a liquid-filled sac was observed on the ventrolateral border of the right uterine horn. The sac was ligated and excised. The uterine horns and ovaries were stained for histopathological evaluation. Granulosa cell tumor (GCT), adenomyosis (CUA), endometrial cystic hyperplasia (CEH), and uterine serosal inclusion cyst (USC) were diagnosed through histopathology assessment. Following up, 12 weeks after surgery revealed that the patient was in good condition with a good appetite and without any vaginal discharge. It seems the initial problem of the present bitch and the main cause of clinical signs was GCT. Probably, other abnormal conditions including CUA, CEH, and USC occurred as a result of hormonal disturbance associated with GCT. This report described the concurrent occurrence of GCT, CUA, CEH, and USC in a bitch as it has not been reported before.

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Introduction

Ovarian tumors are not very common in the bitches. Others suggested the occurrence of granulosa cell tumor (GCT) as the most common, second most common and uncommon ovarian tumors in entire bitches.¹⁻⁴ Many synonyms are defined for GCT, including granulosa-theca cell tumor, feminizing mesenchymoma, gynoblastoma, folliculoma, granulosa cell carcinoma, basal cell tumor of the ovary, follicular adenoma or follicular epithelioma.³ Sex cords or primitive cortical lobules and the specialized stroma or mesenchyme of the developing gonad can potentially originate GCT.²⁻⁴ GCT can produce many hormones which cause a variety of clinical signs including the nipple and vulvar enlargement, discharge, persistent estrus or pancytopenia (due to estrogen production), or cystic endometrial hyperplasia and pyometra (due to progesterone production).¹⁻⁴ In other words, the proliferation of the uterine glands and penetration to the myometrium can result in adenomyosis. Canine uterine adenomyosis (CUA) is reported in the literature.^{5,6}

The CUA is uncommon and commonly found during other uterine pathologic changes including endometritis, pyometra, or cystic endometrial hyperplasia (CEH).⁷ The CEH is most common among the cystic lesions of the canine uterus and is most frequently associated with pyometra.⁸ The CEH is a chronically developing degenerative disease of the endometrium that is triggered by progesterone during metestrus.^{9,10} Cystic endometrial hyperplasia is endometrial thickening caused by an increase in the size and number of endometrial glands.¹¹ Many reports suggested the concurrent occurrence of CUA with GCT or CEH with GCT.^{3,6} To the author's knowledge, the concurrent occurrence of GCT, CUA, and CEH have not been reported in the bitch. Hence, the present report aimed to perform and describe the pathological study of the mentioned lesions in a bitch.

Case Description

An eleven-year-old Doberman-German Shepherd mixed breed bitch, weighing 27.00 kg, was referred to the

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Veterinary Teaching Hospital of the Shahid Chamran University of Ahvaz. She was presented for vulvar enlargement, vaginal discharge, and bleeding for two months and a week before, respectively. Bleeding was discontinuous. History taking revealed that she did not have experienced mating and pregnancy. Physical examination was carried out with any major abnormalities. A blood sample was collected for routine complete blood count (CBC) and revealed all parameters within the normal ranges. Since endometrial abnormality was the probable major problem and according to the age of the bitch with the consent of the owner, she was elected for ovariohysterectomy. Initially, she was sedated using 0.10 mg kg⁻¹ acepromazine (Alfasan, Woerden, The Netherlands). Then, an angiocatheter was inserted and fixed in the left cephalic vein. After the abdominal region was clipped and prepared for aseptic surgery, anesthesia was induced using a mixture of 0.20 mg kg⁻¹ diazepam (Caspian Tamin Pharmaceutical Co., Rasht, Iran) and 10.00 mg kg⁻¹ ketamine (Alfasan) through the angiocatheter. Then, intubation was applied to have a patent airway. Routine midline celiotomy was approached, and the ovariohysterectomy was done using the routine method. The dog was medicated using cefazolin (22.00 mg kg⁻¹; IM; Exir Pharmaceutical Co., Borujerd, Iran) twice a day for five days to prevent infection. Ketoprofen (3.00 mg kg⁻¹; IM; Razak Laboratories, Karaj, Iran) was given daily for three days to control pain and inflammation. During the surgery, a sac containing some of the colorless liquid was observed on the ventrolateral border of the right uterine horn (Fig. 1A). The sac was ligated and excised. The uterine horns were harder than usual and their appearance was the same as small intestines. Also, a hard mass about 0.50 × 0.50 cm in size and without any different color to the surrounding tissues was palpated on the right ovary. Both uterine horns with connected ovaries

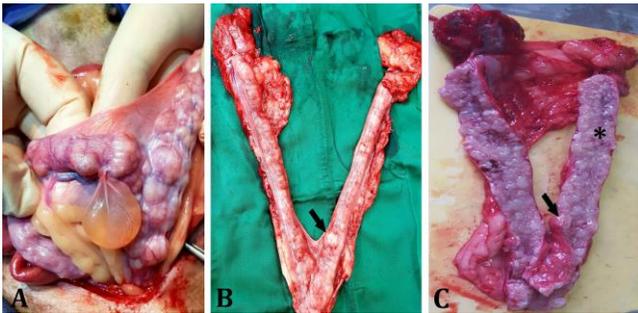


Fig. 1. **A)** Liquid filled sac located on the ventrolateral border of the right uterine horn. **B)** Overview of ovaries and uterine horns of the eleven-years-old Doberman-German Shepherd mixed breed bitch. Note a distinct nodule that is obvious from uterine serosa (arrow). **C)** The endometrial surface of the uterus. Note the existence of many cysts with different sizes in the endometrium (asterisk). Also, no discharge was observed. A mass, which is obvious from uterine serosa and endometrium (arrow), is observed.

(Fig. 1B) were fixated in 10.00% buffered formalin and routinely prepared and stained with Hematoxyline and Eosin for light microscopy.

The macroscopic examination of the right ovary revealed a big cyst filled with brown and jelly materials. The gross appearance of uterine endometrium evidenced it was filled by many cysts. They had different sizes and some of them were filled by clear fluid. No discharge was seen on the surface of the endometrium (Fig. 1C). Also, a mass was seen between cysts on the left uterine horn endometrium (Fig. 1C). It was around 1.00 cm and its cut surface was white and solid.

In the microscopic examination of the ovary, proliferated cells covered the wall of the cyst and was filled with protruded neoplastic cells and hemorrhage (Fig. 2). Different patterns such as cords, trabeculae, and nest were observed (Fig. 3). Proliferated cells were separated and supported by fine connective tissue. They had round to oval basophilic nuclei with prominent nucleoli. Call-Exner bodies with eosinophilic material surrounded by a sheet of neoplastic cells were observed (Fig. 4). According to mentioned microscopic characteristics, granulosa cell tumor was diagnosed.

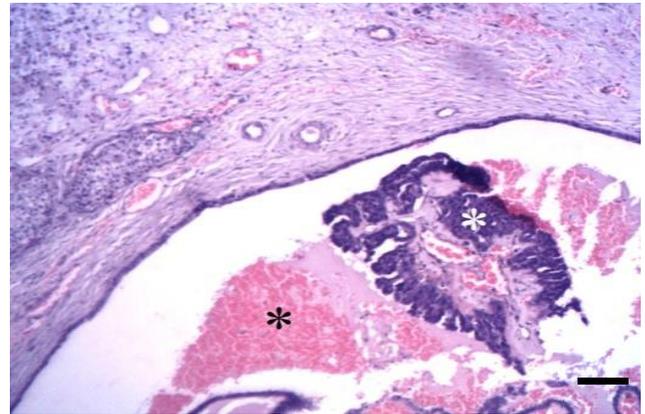


Fig. 2. Granulosa cell tumor, ovary. Note the existence of hemorrhage (black asterisk) and proliferated cells in the lumen of the cyst (white asterisk) (H&E; Scale bar = 200 µm).

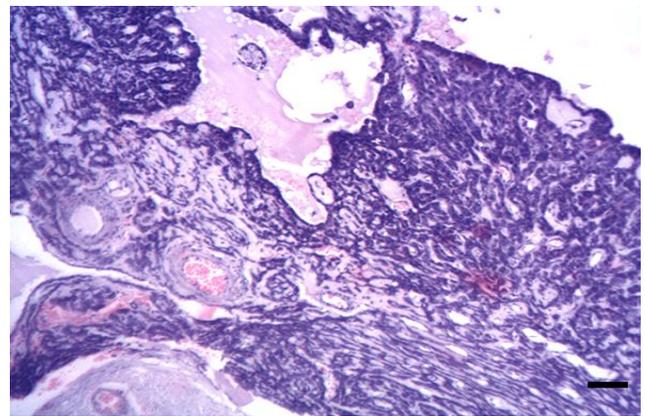


Fig. 3. Granulosa cell tumor, ovary. Note the cord pattern of neoplastic cells (H&E; Scale bar = 200 µm).

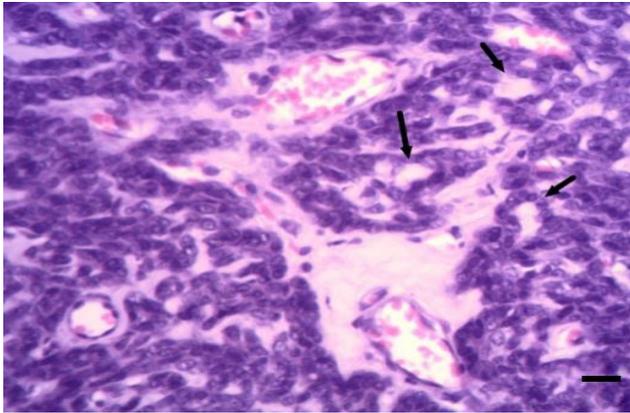


Fig. 4. Granulosa cell tumor, ovary. Note the Call-Exner bodies (arrows). Neoplastic cells are radially located around the eosinophilic center (H&E; Scale bar = 200 μ m).

Histopathologic examination of uterine revealed cystic endometrial hyperplasia. Multiple and large cysts were observed in the endometrium (Fig. 5A). Some of the cysts were filled with pink materials. They were covered by one layer of cuboidal to columnar cells (Fig. 5B). The microscopic examination of the mass, observed in the uterine, revealed adenomyosis. It was characterized by the existence of proliferated endometrial gland cells among bundles of the myometrium. Gland cells were among cuboidal to columnar cells. The lumen of glands showed different sizes, and some of them were cystic (Fig. 6A).

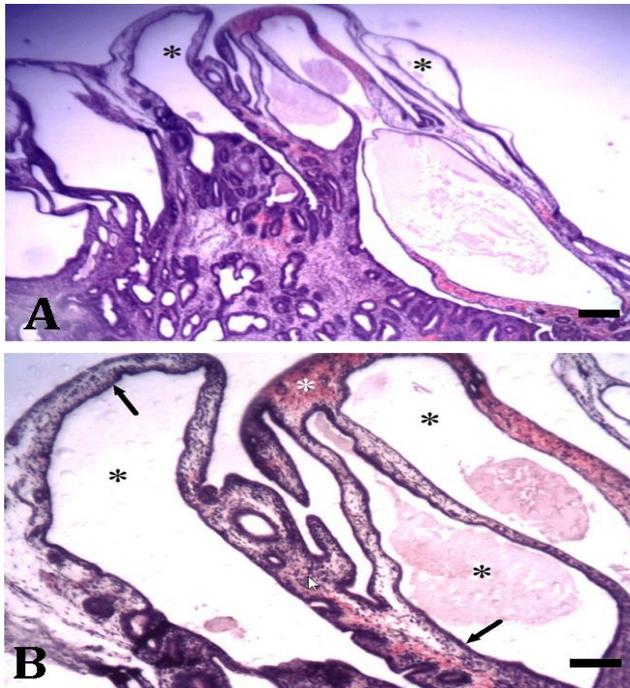


Fig. 5. Cystic endometrial hyperplasia, uterus. **A)** Note multiple and large cysts (asterisk) in endometrium. Some of them are filled with eosinophilic materials. **B)** Cyst (black asterisks) are covered by one layer cuboidal cells (arrows). Hemorrhage is obvious between cysts (white asterisk), (H&E; Scale bars = 200 μ m).

Glands were covered by columnar cells. The cells had columnar nuclei with prominent nucleoli in the base of cells (Fig 6B).

Phone contact with the owner every two weeks and then monthly after surgery up to four and sixteen weeks, respectively, revealed that the patient was in good condition with a good appetite and without any vaginal discharge. The owner reported that the vaginal discharge was stopped three days after surgery.

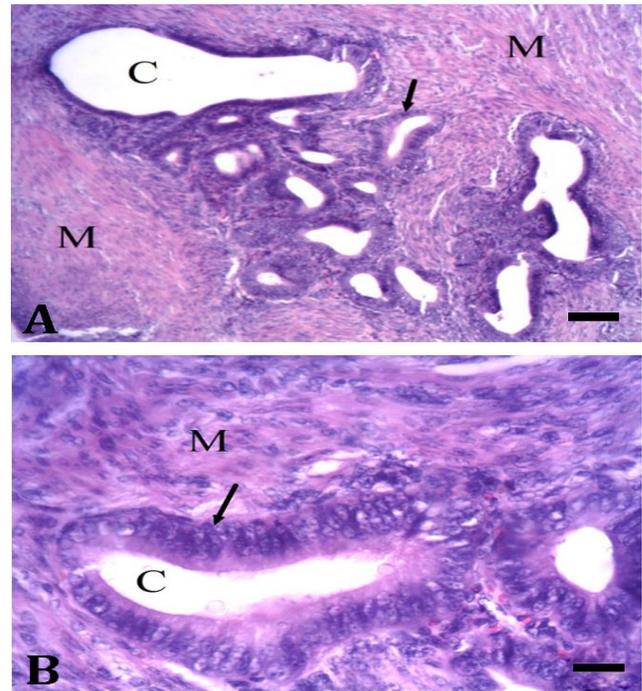


Fig. 6. Adenomyosis, uterus. **A)** Note the infiltration of proliferated endometrial gland cells (arrow) among bundles of the myometrium (M). Some glands are cystic (C). **B)** Glands (C) which are located among bundles of the myometrium (M) are covered by columnar cells (arrow). Proliferated cells have columnar nuclei with prominent nucleoli in the base of cells. (H&E; Scale bars = 200 μ m).

Discussion

Endocrine-related tumors are a common cause of hormonal dysregulation and GCT is one of the probable tumors in bitches.^{6,10} GCTs produce estrogens (2.00 to 35.00 nmol L⁻¹) and small amounts of progesterone (180 to 600 pmol L⁻¹) responsible for the clinical signs are associated with this tumor and subsequent problems.^{12,13} GCTs are usually unilateral and the left ovary is more commonly affected.¹³ Unilateral GCTs are rarely metastatic (< 20.00%).² Ninety-five to 100% and 63% of bitches suffering from GCTs are followed by CEH and pyometra, respectively.² However, in the present report, GCT was diagnosed in the right ovary and the majority of the clinical signs were assumed to be related to this tumor, initially. Also, CEH without pyometra was diagnosed pathologically.

On the other hand, hormonal disturbances have a major role in CUA and CEH.^{6,13} The secreted progesterone can enhance endometrial growth and develop CEH and CUA.¹³ Chronic and repeated progesterone stimulation, are thought to lead to the exaggerated endometrial response characteristic of CEH.¹¹ It might be speculated that the presence and development of the CUA and CEH in the present bitch, was after the GCT. CUA frequently occurs with other estrogenic conditions such as CEH, suggesting that it is associated with hyperestrogenic states.⁸ Uterine serosal inclusion cysts (USC) are structures arising from mesothelial cells when they become trapped in the serosa.¹⁴ USC are solitary or multifocal and incidentally found during ovariohysterectomy in dogs.⁸ The cysts do not have any effect on fertility, however, sometimes it may be associated with hormonal dysfunction.¹⁵ It seems the liquid-filled sac on the uterine horn was USC, although the specimen was missed during surgery and histopathology evaluation was not processed. USC is found mostly in old mixed breed bitches and is usually focal than disseminated.¹⁴ In the present case, the bitch was eleven years old mix breed with a focal cyst.

In agreement with the present case, about 80% of GCTs are benign.³ Although ovariohysterectomy was applied for the present case without having a confirmatory diagnosis, the treatment of choice for GCT is ovariohysterectomy.³ The histopathological diagnosis of GCT is easily mistaken for ovarian epithelial tumors.²

Although radiographic and ultrasonography examinations could benefit the diagnosis, results, and discussion, unfortunately, these evaluations were not carried out.

Several hormones including endogenous progesterone, estradiol, have proliferation-inducing effect and are defined as a risk factor.¹⁰ Proliferative changes in the reproductive system could result from continuous exposure to steroid hormones and the uterine epithelium may be prone to develop neoplasia in early life.¹⁰ Maybe the serial hormonal level assessment prior and postoperatively, could open a better view to manage the patient, however, the hormonal level assessment was not applied.

In conclusion, it seems the initial problem of the present bitch, and the main cause of clinical signs was GCT. Probably, other abnormal conditions including CUA, CEH, and USC have occurred as a result of hormonal disturbance associated with GCT. This report described the concurrent occurrence of GCT, CUA, CEH, and USC in a bitch as it has not been reported before.

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Conflict of interest

The authors declare no conflict of interest.

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