한국가축위생학회지 제36권 제2호 (2013)
Korean J Vet Serv, 2013, 36(2), 127-132
ISSN 1225-6552, eISSN 2287-7630
http://dx.doi.org/10.7853/kjvs.2013.36.2.127

Korean Journal of
Veterinary Service
Available online at http://kjves.org

< Short Communication >

A case of canine bilateral ovary granulosa cell tumor and mammary complex carcinoma

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(Received 5 February 2013; revised 1 May 2013; accepted 8 May 2013)

Abstract

An 11-year-old poodle bitch was presented for investigation of multicentric mammary masses. Abdominal sonography and radiography demonstrated abnormal enlargement of uterus and ovaries. Blood analysis revealed high progesterone concentration. The ovariohysterectomy and mastectomy were performed. Histopathologically, the mammary masses revealed complex carcinoma-tubulopapillary carcinoma with papillary pattern and tubule pattern. In the uterus, cystic endometrial hyperplasia was observed. Scattered inflammatory cells were observed in the endometrial stroma and mucinous material was protruded from endometrial surface. Also, in the ovaries, bilateral ovary granulosa cell tumor was detected. The bitch made a complete recovery following the ovariohysterectomy and mastectomy. This case was a very rare multiple tumor occurrence with bilateral ovary granulosa cell tumor and mammary complex carcinoma. High progesterone concentration was characterized clinically in the bitch.

Key words : Endometrial cystic hyperplasia, Granulosa cell tumor, Mammary complex carcinoma, Dog

INTRODUCTION

A wide variety of pathogenic changes occur in and around the ovary (McEntee 1990; McLachlan, 1987). Affected animals, especially bitches, may show marked manifestation of hyperestrogenism such as altered reproductive behavior, anemia, and hemorrhagic diathesis (MacLachlan and Kennedy, 2002). Ovarian tumors are derived from three main cell types: epithelial, germ, and sex-cord stromal cells (Patnaik and Greenlee, 1987). Granulosa cell tumors are a type of sex cord stromal tumors such as Sertoli-Leydig cell tumors and luteomas (McCandlish et al, 1979). Granulosa cell tumors are usually unilateral and the left ovary is more commonly affected (Purswell et al, 1999). Ovarian tumors produce steroid hormones or estrogen that influence the clinical signs associated with ovarian tumors (McCandlish et al, 1979; Purswell et al, 1999).

Cystic endometrial hyperplasia (CEH) and pyometra in the bitch are diestral syndromes, supposed to be caused by hormonal disturbances and changes in endometrial steroid hormone receptor levels (Leitner et al, 2002). Histologically, the endometria show cystic dilated glands and, if bacteria succeed in invading the uterus, pyometra may develop in the following metoestrus (Kim and Kim, 2005). The occurrence of CEH has been reported in connection with the administration of progesterone-related contraceptives in cats and zoo animals (Munson et al, 2002).

Complex gland tumor is uncommon lesions in the human breast, but they are found most frequently in the mammary gland of the female dogs (Vail and MacEwen, 2000). Recently, the tumors were increased and the mammary tumors particularly were investigated in Korean veterinary clinics (Kim and Kim, 2005). The mammary tumor is first epidemiological issue in oncol-

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Table 1. Blood analysis of a dog (K2011037) with multiple tumors and cystic endometrial hyperplasia

Parameter*	RBC	WBC	Platelet	ALB	ALP	ALT	TBIL	BUN	CRE	GLU	TP
Normal Range	5.5～8.5 ($\times10^6$/μl)	6～17 ($\times10^3$/μl)	200～900 ($\times10^3$/μl)	2.5～4.4 (g/dl)	20～150 (U/L)	10～118 (U/L)	0.1～0.6 (mg/dl)	7～25 (mg/dl)	0.3～1.3 (mg/dl)	60～110 (mg/dl)	5.4～8.2 (g/dl)
Data	7.5	21	850	3.5	120	95	0.5	18	0.9	90	5.0

*ALB: albumin, ALP: alkaline phosphatase, ALT: alanine aminotransferase, TBIL: total bilirubin, BUN: blood urea nitrogen, CRE: creatinine, GLU: glucose, TP: total protein.

ogy of both female dogs and human. Mammary tumor is the most common malignant tumor and represents 50% of total neoplasm case in dogs (Vail and MacEwen, 2000). In cats and dogs, the term complex mammary gland tumor (Misdorp, 2002) is alternatively used and defines a tumor with both epithelial and myoepithelial origins either benign (complex adenoma) or malignant (complex carcinoma). The mammary tumor of this case was occurred at relatively early age as compared with a median age of occurrence of 10～11 years in dogs (Schafer et al, 1998).

Here, we report a very rare multiple tumor occurrence with bilateral ovary granulosa cell tumor and mammary complex carcinoma in a female dog.

CASE REPORT

An 11-year-old poodle was presented for investigation of multicentric mammary masses. The bitch had not treated with hormone contraception or hormone replacement therapy. Blood analysis indicated the slight decrease of total protein and slight increase of WBC (Table 1). Urine analysis revealed mild protein loss. Blood samples were collected from the jugular vein and centrifuged at 4°C for 10 min at 1,500 g. Plasma sample for progesterone and estradiol determination were analyzed the same day. The results of plasma analysis revealed high progesterone concentration (Table 2). Abdominal sonography and radiography demonstrated abnormal enlargement of right horn of uterus, and the ovariohystectomy and mastectomy were performed.

The mammary masses were solid, firm and measured 3～6 cm in diameter (Fig. 1A). Gross examination of the surgical operated uterus revealed enlarged lesions in the right horn. The uterus had thickened wall and yellowish sticky material in the lumen (Fig. 1B). Also, ovaries showed swelling, which had white and firm areas on the dissected surface (Fig. 1C). The trimmed tissues were fixed in 10% neutral buffered formalin, and embedded in paraffin. Tissue sections were made and stained with hematoxylin and eosin for histopathological examination.

Table 2. The concentrations of estradiol and progesterone in jugular venous blood

Serum origin	Before orchidectomy	
	Estradiol (pmol/L)	Progesterone (nmol/L)
Normal control*	38.6	8.5
K2011037	38.2	18.2

*Hormone concentrations were also measured with the blood collected from other poodle, who was 11-year-old female dog and had no ovarian tumor.

Histopathologically, the mammary masses revealed tumor cells originated from mammary gland cells. The mammary masses revealed complex carcinoma - tubulopapillary carcinoma with papillary pattern and tubular pattern. The tumor displayed multiple duct-like structures, which were filled with coalescing multibranched papillae (Fig. 2). Collagenous connective tissue stalks supported the papillae. Covering the papillae were irregular stratifications of epithelial cells with considerable loss of polarity. The epithelial cells were columnar and had large round hyperchromatic nuclei and variable numbers of mitotic figures. The nucleoli were generally solitary and enlarged. Some papillae were fused and converted solid cellular masses that exhibited necrosis of tumor cells centrally. On the other hand, in the ovaries, ovary granulosa cell tumor was detected (Fig. 3). Neoplastic cells are columnar to angular and have a variable amount of foamy to vacuolated eosinophilic cytoplasm. Nuclei are oval with occasional mitotic

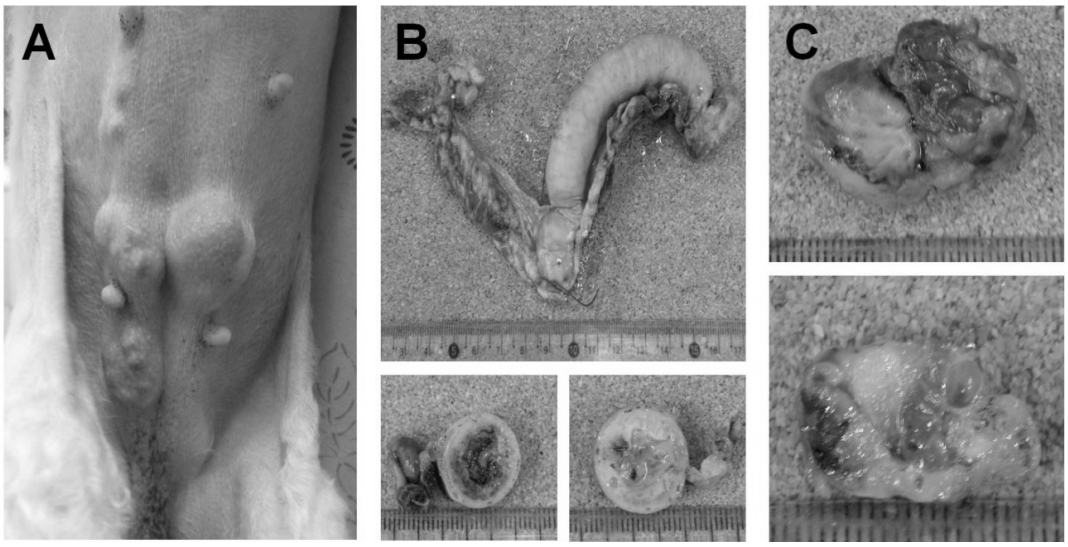

Fig. 1. Gross photograph. (A) Mammary masses, (B) Detectomized uterus (bottoms: cut surface), (C) Detectomized ovaries (upper: left ovary, bottom: right ovary).

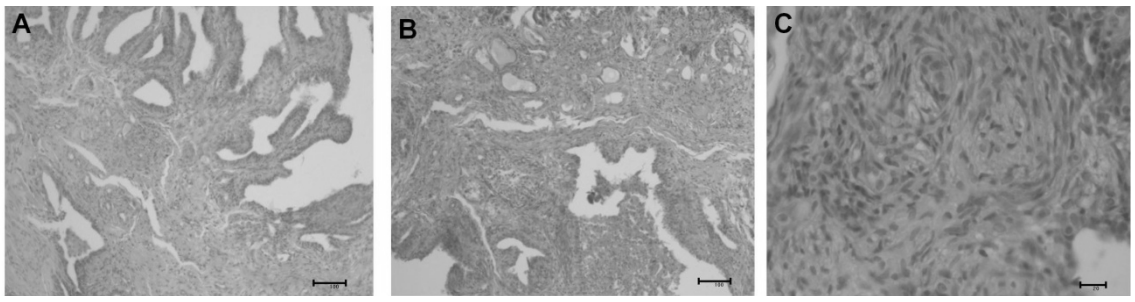

Fig. 2. Histopathological findings of mammary masses. Mammary complex carcinoma was diagnosed. H&E stain, (A) ×100 (bar = 100 μm), (B) ×100 (bar = 100 μm), (C) ×400 (bar = 20 μm).

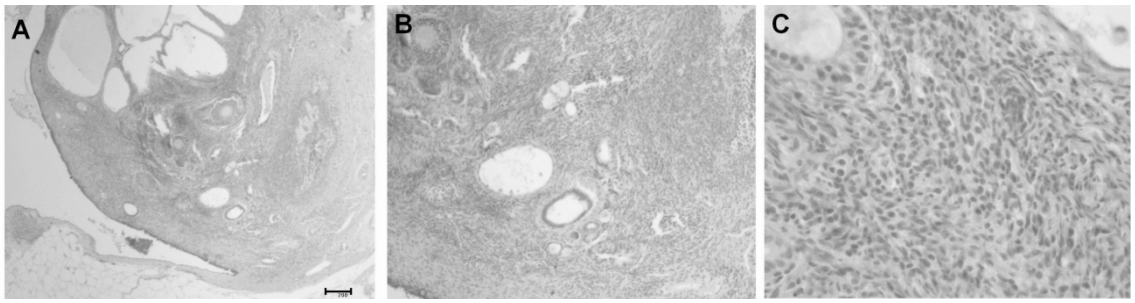

Fig. 3. Histopathological findings of ovaries. Ovarian granulosa cell tumor was diagnosed. H&E stain, (A) ×40 (bar = 200 μm), (B) ×100, (C) ×400.

figures. High-magnification photomicrograph of a canine ovarian granulosa cell tumor displaying a tubular growth pattern in which variably sized tubules are separated by a dense fibrovascular stroma. Also, in uterus, CEH and endometritis were present in the thickened area (Fig. 4). The most prominent endometrial lesion was CEH, characterized by dilated cystic glands, glandular proliferation in adenomatous clusters, or hyperplasia of the surface endometrium resulting in irregular folds or polypoid projections into the lumen (Fig. 4). Cystic glands were

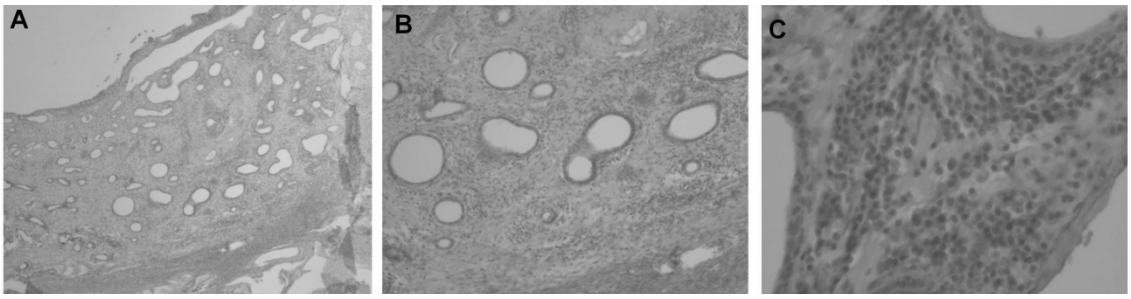

Fig. 4. Histopathological findings of of uterus. The most prominent endometrial lesion was cystic endometrial hyperplasia, characterized by dilated cystic glands. H&E stain, (A) ×40, (B) ×100, (C) ×400.

variable in size and were lined by densely packed epithelium that was usually compressed by retained secretory material. Lesions of severe hyperplasia were often accompanied by focal calcification. Scattered inflammatory cells were observed in the endometrial stroma and mucinous material was protruded from endometrial surface.

The bitch made a complete recovery following the ovariohysterectomy and mastectomy. This case was simultaneous ovary granulosa cell tumor and uterine CEH with mammary complex carcinoma.

DISCUSSION

Pathologic changes of the canine endometrium are associated with degeneration of luminal epithelium, CEH, pyometra and adenocarcinoma (Chu et al, 2002). The higher dose level of progesterone derivative like as megestrol acetate induced marked mammary stimulation, hyperplastic and neoplastic changes in the mammary glands. Also, it contributed to clinical and pathologic changes typical of diabetes mellitus (Weikel and Nelson, 1977). Side effects of exogenous progesterones were focused on induction of mammary tumors. Although progesterone counteracts the proliferative effects of estrogen and protects against endometrial hyperplasia (Pazol et al, 2004), it has been reported that progesterone and its derivatives may increase CEH risk in uterus (Munson et al, 2002). Prolonged exposure to megestrol acetate has been associated with CEH and pyometra in domestic cats and progesterone contraceptives may have similar effects on zoo fields (Pazol et al, 2004). Megestrolacetate acetate is a derivative of progesterone and used commonly both in contraception and hormone replacement therapy (Pazol et al, 2004). Due to available clinical and epidemiological data, it has been long suspected that tumors of the female genital tract of the dog develop under the influence of ovarian hormones (Klein, 2001). Canine genital tract tumors have been observed to have both estrogen receptor-α and progesterone receptors, just as both human and feline genital tumors (Bodner et al, 2004; Martín De Las Mulas et al, 2000; Millán et al, 2007). Most sources describe that canine mammary tumors are age dependent, rarely occurring before 5 years of age (Cohen et al, 1974). Granulosa cell tumors appear to arise from granulosa cell cords derived from atretic follicles (McEntee, 1990). Granulosa cell tumors are capable of producing estrogens and small amounts of progesterone (Davidson and Feldman, 2005). In most cases of granulosa cell tumors, the clinical signs are referable to increased estrogen and progesterone synthesis and to a lesser extent to the mass effect of the tumor. The progesterone secreted by the granulosa cell tumors enhances endometrial growth and glandular secretion, which can lead to the CEH-pyometra complex (Feldman and Nelson, 1987). It has been demonstrated in humans that granulosa cell tumors express gonadotropin receptors (Stouffer et al, 1984) and respond to gonadotropins (Graves et al, 1985). In this regard, it has been speculated that gonadotropins may be involved in the pathogenesis of granulosa cell tumors.

In this study, the bitch had multiple tumors and CEH, which were composed of the different types of tumors and pathogenic changes like as mammary complex carcinoma and uterine CEH and ovary granulosa cell

tumor. The dog had not been fed with a derivative of progesterone like as megestrol acetate which used commonly both in contraception and hormone replacement therapy. We thought that the multiple tumors and uterine CEH of this case report were probably related to ovarian granulosa cell tumor, although it could not be ruled out that other factors such as old ages contributed to induce this simultaneous occurrence of multiple types of tumors. The bitches with ovarian tumors may show marked manifestation of hyperestrogenism (MacLachlan and Kennedy, 2002). In this case, high concentration of progesterone was detected. These hormonal imbalances may be resulted in the induction of multiple types of tumors in the bitch.

This report describes a case of multiple tumors and uterine CEH in a bitch. To our knowledge, this report is a rare case of multiple tumors with mammary complex carcinoma and uterine cystic endometrial hyperplasia and bilateral ovary granulosa cell tumor. The uterine CEH and mammary tumors are frequently associated with ovarian hormone-secreting tumors in animals and human (Bodner et al, 2004; Martín De Las Mulas et al, 2000; Millán et al, 2007). However, there is as yet no precise knowledge of the role of progesterone and estrogen in tumorigenesis of the uterus. This case was a very rare multiple tumor occurrence with bilateral ovary granulosa cell tumor and mammary complex carcinoma. High progesterone concentration was characterized clinically in the bitch.

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