Journal of the Hellenic Veterinary Medical Society

Vol 69, No 2 (2018)

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doi: 10.12681/jhvms.18022

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To cite this article:

GÜNAY UÇMAK, Z., UÇMAK, M., TEK, Ç., KOENHEMSI, L., ERDOGAN BAMAÇ, Ö., GÜREL, A., & YILDAR, E. (2018). Granulosa Cell Tumor In A Spayed Young Queen. *Journal of the Hellenic Veterinary Medical Society*, *69*(2), 1010–1015. https://doi.org/10.12681/jhvms.18022

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J HELLENIC VET MED SOC 2018, 69(2): 1010-1015
ΠΕΚΕ 2018, 69(2): 1010-1015

Case Report
Κλινικό Περιστατικό

Granulosa Cell Tumor In A Spayed Young Queen

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ABSTRACT. A four years old cat was presented to Clinic of Obstetrics and Gynaecology with complaints of weakness, inappetency, vomiting and estrus signs although it was spayed. Blood tests, radiography and ultrasonography revealed abdominal mass and uterine stump which were then removed surgically. Multilobular mass was defined as solid granulosa cell tumor (GCT). Increase of estrogen (E2) and insulin-like growth factor-1 (IGF-1) values were detected on the 10th postoperative day. On the 40th postoperative day, the cat was brought to Internal Medicine Clinic with the complaints of weakness, inappetency and cachexia. Anemia, leucocytosis, uremia, hyperglycemia, sensitiveness and pain in the right abdomen were determined. A tumor was detected in the liver by radiography and ultrasonography and was suspected to be GCT metastasis. Despite medical therapy, the cat died after four months.

In conclusion; retained ovarian tissue after erroneous ovariohysterectomy may cause, regular estrus signs and GCT development. Even if GCTs are removed by surgical approach, they have metastatic potential that deteriorates the prognosis. Evaluating IGF-1 and E2 in the short postoperative term are beneficial for determining the metastatic potential of GCTs.

Keywords: Granulosa cell tumor, IGF-1, estrogen, ovary, queen.

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Date of initial submission: 4-4-2017
Date of revised submission: 2-8-2017
Date of acceptance: 21-8-2017

CASE HISTORY

A four-years-old female cat, that was spayed when was one year old at a private clinic, was brought to Obstetrics and Gynaecology Clinic with regular estrus signs for three years. The cat had received a treatment because of vomiting, anorexia and weakness for 15 days beforehand in a proprietary clinic.

Complete blood cell count (CBC), ALT (Alanine aminotransferase), AST (Aspartate aminotransferase), ALP (Alkaline phosphatase), GGT (Gama glutamyl transpeptidase), urea, creatinine, glucose, cholosterol, IGF-1, E2, progesterone (P4) analysis, thoracoabdominal radiography and abdominal ultrasonography were performed. Blood parameter results on operation day are notified in Table 1.

On ultrasonographic examination, a mass was viewed behind the left kidney (Figure 1a.,1b.) and uterine stump was determined. On radiography there was no visible metastasis in thorax; however the abdominal mass was clearly seen (Figure 2). A surgical approach was decided.

The anesthesia protocol consisted of sc atropine (Atropin, Vetaş, Turkey) as premedication (0.005 mg/kg) followed by the induction of the anesthesia 15 min. later with iv propofol (Pofol 1%, Dongkook Pharm, Korea) (6 mg/kg), and the intubation and maintenance with 3% isoflurane (Forane likid, Abbott Laboratories, England). Uterine stump (Figure 3) and a mass sized 12x10x5 cm which was located behind left kidney, around the left ovary, were removed by

Table 1. Blood parameter results on operation day and postoperative 10th, 40th and 45th day.

Blood Parameters		Referance Ranges In Cats	Operation Day	Postoperative 10th Day	Postoperative 40th Day	Postoperative 45th Day
RBC		5.8-11 uL*	4.5	6.84	4.5	3.6
HGB		8.6-16 g/dl*	6.5	9.6	6.3	4.6
HCT		28-47%*	20	31	18	14
WBC		(3.7-20.5) x1000/uL*	51.5	14.7	55.8	51.6
PLT		(160-660) x1000/uL*	494	386	95	157
MCV		37.7-50 fL*	45	46	39	40
MCH		12.3-17.2 pg*	15	14	14	13
MCHC		(31.1-36) x10 g/L*	32	31	36	32
GLU.		56-153 mg/dL*	224	164	170	190
UREA		18-36 mg/dL*	71	57	56	61
CREA.		0.6-2 mg/dL*	0.7	0.6	0.6	0.4
AST		14-54 U/L*	17	34	22	19
ALT		26-128 U/L*	26	51	28	20
ALP		14-102 U/L*	90	41		
GGT		0-5 U/L*	1	1		
Cholesterol		71-218 mg/dL*	134	165		
IGF-1		5-70 nmol/L**	88	118		
E2	Base level	5-14 pg/ml***	56.2	67.1		
	In estrus	50-70pg/ml***				
P4	Luteal phase	1-4 ng/ml***	0.48	0.37		
	In estrus	< 1ng/ml***				

RBC= Red Blood Cell Count; HCT= Hematocrit; HGB= Hemoglobin; MCV= Mean Corpuscular Volume; MCH= Mean Corpuscular Hemoglobin; MCHC= Mean Corpuscular Hemoglobin Concentration; WBC= White Blood Cell Count; PLT = Platelet Count; CREA= Creatinine; GLU= Glucose; AST= Aspartate Aminotransferase; GGT= Gamma Glutamyltransferase; ALP= Alkaline Phosphatase; ALT= Alanine aminotransferase; IGF-1= Insulin-like growth factor-1; E2= Estrogen; P4= Progesterone. Reference values: *Plumb (2008), **Maden and Çuhadar (2013), ***Shille et al., (1979).

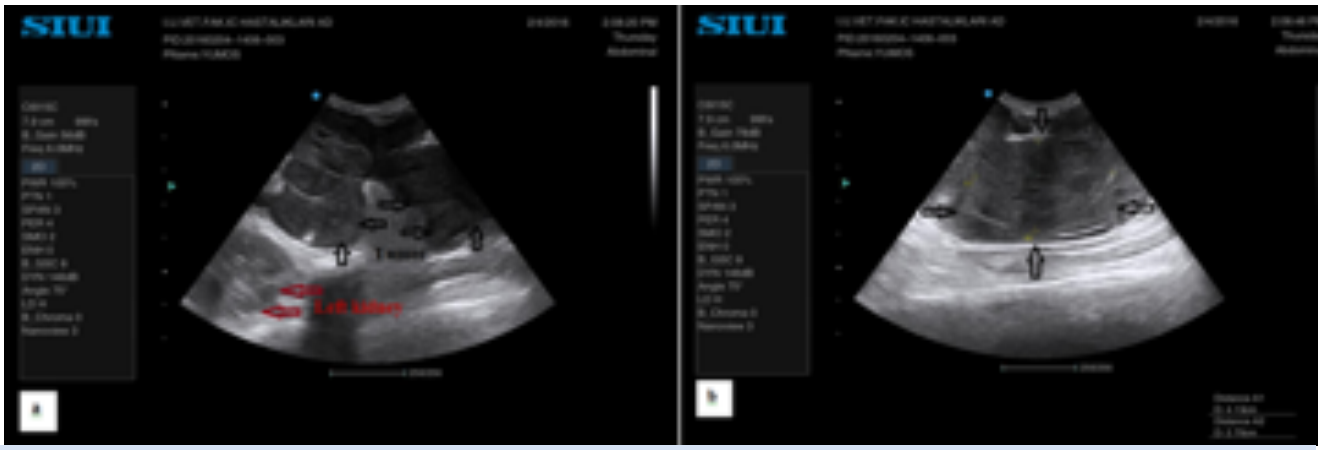

Figure 1a. The mass behind left kidney on cranioabdominal regio, **1b** Tumoral mass on ultrasonographic examination.

Figure 2. Tumoral area on thoraco-abdominal radiography of the cat.

Figure 3. Uterine stump

median laparotomy. Before laparotomy incision was closed, we were sure that there was no residual ovarian tissue in the abdomen. Monofilament and absorbable suture material (Monocryl No: 2/0, Medeks, Turkey) was used for ligations, muscular, subdermal and dermal sutures. The mass and stump uterus were delivered to Pathology Department for histopathologic examination. Twenty ml/kg iv 0.9 % isotonic sodium chloride twice a day (b.i.d), 20 ml/kg iv Lactated Ringer (Laktatlı Ringer, Polifarma, Turkey) b.i.d., 40 µg/kg intramuscular (im) vitamin B12 (Dodex, Deva, Turkey) once daily (s.i.d.), B and C complex vitamin (Hepargriseovim, Deva, Turkey), 20 mg/kg im ampicillin sodium (Ampisina, Mustafa Nevzat, Turkey) b.i.d. and 15 mg/kg im clindamycin (Klindan, Bilim, Turkey) b.i.d. were administrated to the cat for ten days postoperatively. Also inactivated parapoxvirus ovis (Zylexis, Pfizer, USA) was injected once a week for four weeks by subcutaneous way.

The first control was made on the 10th postoperative day. On anamnesis; having appetite, absence of vomiting and vitality were informed. Blood parameter results on the 10th postoperative day are notified in Table1. After isotonic serum infusion and low protein diet for seven days, blood profile was as follows; hematocrit 28%, hemoglobin 8.6 g/dl, glucose 166 mg/dl, urea 45 mg/dl and creatinine 0.7 mg/dl. According to this blood profile, 0.9% isotonic sodium chloride (Izotonik, Eczacıbaşı, Turkey), Lactated Ringer (Laktatlı Ringer, Polifarma, Turkey), B and C vitamin complex (Hepargriseovim, Deva, Turkey) and vitamin B12 (Dodex, Deva, Turkey) were administrated. Three weeks after the prescrip-

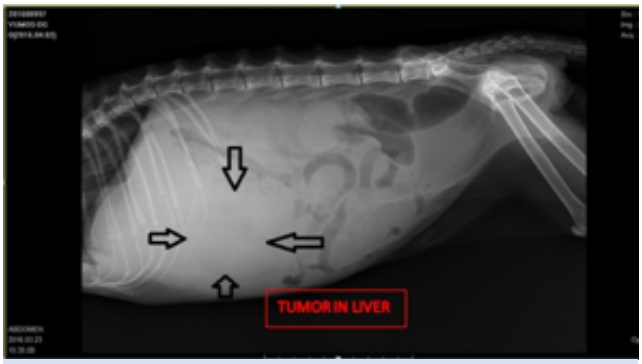

Figure 4. Abdominal radiography of the tumor in liver.

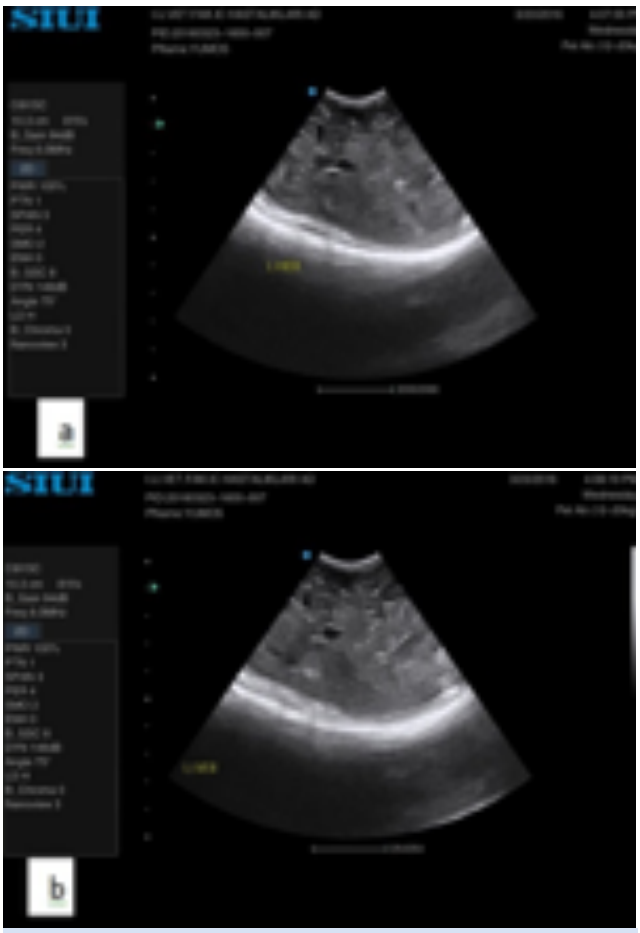

Figure 5a,b Hyperechoic areas within liver on ultrasonography.

tion applied, the cat was brought again to Internal Medicine Clinic with the complaint of weakness, anorexia and cachexia. Anemia, leucocytosis, uremia and hyperglycemia were detected on the 40th postoperative day (Table 1). As a result, 20 mg/kg ampicillin sodium and sulbactam combination (Sulcid, İ.E. Ulagay, Turkey), 15 mg/kg clindamycin (Klindan,

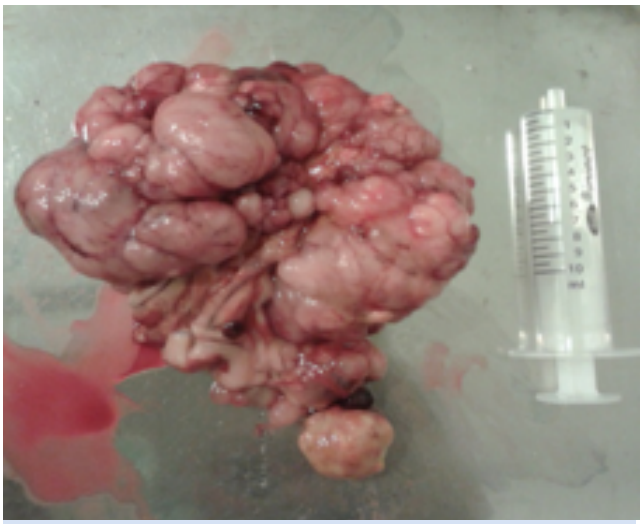

Figure 6. Tumoral mass in macroscopic examination.

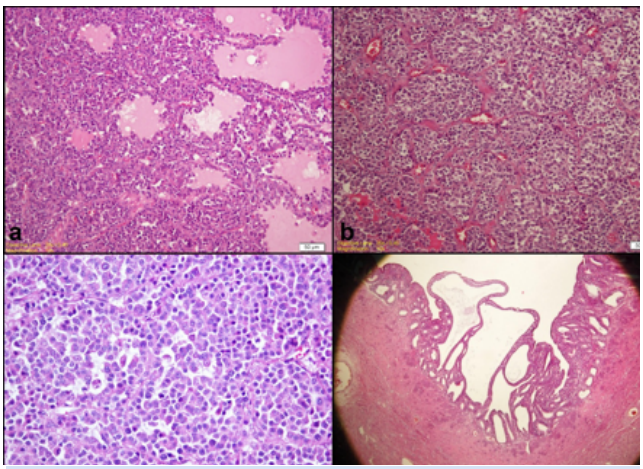

Figure 7a Cystic structures with diffuse, atypical granulosa cells. **7b, 7c** Density of distinctive tubuler pattern in stroma. **7d** Cystic glandular metritis.

Bilim, Turkey) and vitamin B12 (Dodex, Deva, Turkey) were prescribed for 5 days. At the end of this therapy, blood tests (Table 1) were repeated. Because signs of pain were detected on palpation of the right abdominal region, abdominal radiography (Figure 4) and ultrasonography (Figure 5a,b) were performed. According to ultrasonographic examination, a tumor on the liver was determined. Because of the poor prognosis, surgery was not performed. Medical therapy with 25 mg/kg im Seftriaxon (Novosef, Zentiva, Turkey), 15 mg/kg im clindamycin (Klindan, Bilim, Turkey), 0.9% iv isotonic sodium chloride (Izotonik, Eczacıbaşı, Turkey) and 5% iv dextrose (Dekstroz, Eczacıbaşı, Turkey) serum infusion, im vitamin B12 (Dodex, Deva, Turkey) and 16 mg im cortisone

(Prednol, Mustafa Nevzat, Turkey) was applied for 7 days. After that last therapy, survival time was only four months.

Histopathologic examination was performed at Department of Pathology. In the macroscopic examination, the tumoral mass of the ovary was measured 12x10x5 cm in size and had multinodular structure (Figure 6). Tumor samples were fixed in 10% neutral buffered formalin for at least 24 h and 5 μm thick serial sections were cut, deparaffinized, rehydrated with water in descending concentrations of ethanol and used for hematoxylin and eosin (HE) staining. Tissues were observed under a light microscope. The histological evaluation revealed diffuse, atypical, granulosa-like cells with spherical to oval, hyperchromatic nuclei, distinct nucleoli, and scant eosinophilic cytoplasm. In the diffuse areas, there were cystic structures surrounded by granulosa cells (Fig 7a). Also, a distinctive tubular pattern in which a dense stroma was present (Fig 7b, c). In some slides, areas of luteinisation and hemorrhage were seen. Cystic glandular metritis was also observed in the same patient (Fig 7d).

DISCUSSION

GCTs are the most common sex-cord stromal tumor in all animal species (Nielsen and Kennedy, 1990). Holzworth (1987) reported that mean age of GCT occurrence in cats is 11 years. Contrarily, reported cat which affected with GCT was four years old.

In our case, GCT was detected in a spayed cat as Spoor et al. (2014) detected GCT in spayed Bulldog. In accordance with Gelberg and McEntee (1985), the cat had also estrus signs although spayed in early age. In line with Ball et al. (2010), it is thought to be as a result of incomplete excised ovarian or ectopic ovarian tissues.

Gelberg and McEntee (1985) reported that GCTs are the most common ovarian tumor type in cats which have malignant character. The appearance of the tumor in liver 45 days after the ovarian tumor resection supports GCTs' malignancy as Gelberg and McEntee (1985) reported.

In accordance with Gündüz et al. (2010) ultrasonographic imaging of the ovaries is used for diagnosis of GCT. In line with Hayes and Harvey (1979), we performed surgery for treatment and also after surgery immunotherapeutic agent was used for four weeks.

Noakes (2009) reported that ovariectomy cause elimination of E2, P4, inhibin, activin, and follistatin in ovaries. Shille et al. (1979) notified that E2 in plasma elevate from a base level of 5-14 pg/ml to peaks of 50-70 pg/ml in estrus. Contradicting to Noakes (2009), in this report, we expected base level in plasma E2 after the GCT resection but E2, which was measured 56 pg/ml in the operation day, increased to 62 pg/ml on the 10th postoperative day.

Fontbonne et al. (2007) reported that ovarian remnant syndrome (ORS) leads to elevated levels of ovarian hormones. Shanbhogue et al. (2010) notified that hyperandrogenism and hyperestrogenism are the most common causes of ovarian tumors. Although we had no data about the E2 levels of the erroneous ovariohysterectomized cat before the GCT diagnosis, in line with the researchers (Fontbonne et al. 2007, Shanbhogue et al. 2010) this ORS case was followed by GCT formation.

Buijtels et al. (2010) reported that GCTs produce E2 and small amount of P4 which causes endometrial growth and glandular secretion. In accordance with Buijtels et al (2010), the cat with GCT had high E2 level and also cystic glandular metritis in the uterine stump.

Boormann (2002) notified that increase of E2 levels after surgery happen if a residual hormone producing tumor may exist. Increased E2 levels detected on the 10th postoperative day and presence of tumor on liver 45 days after surgery are in accordance with Boormann (2002).

In accordance with Spicer and Echternkamp (1995), that reported a positive correlation between follicular growth and IGF-1 concentration, IGF-1 concentration was measured high on the operation day in this case.

Despite the resection of GCT and uterine stump, the increased IGF-1 concentration on the 10th postoperative day may be related to IGF-1 synthesis by the metastatic liver as reported (Maden and Çuhadar, 2013).

The histopathological findings of this granulosa tumour did not differ from the literature and they

are in accordance with the aggressive behaviour described for this tumour in cats (Giacóia et al., 1999).

A second operation for tumor resection in liver was not performed due to the poor body condition. It is in accordance with Boormann's (2002) report which defends that second-look operations are unnecessary unless significant masses and complications such as obstruction of the bowel occur.

In conclusion; retained ovarian tissue after erroneous ovariohysterectomy may cause regular estrus signs and GCT development. Even if GCTs are removed by surgical approach, they have metastatic potential that deteriorates the prognosis. Evaluating IGF-1 and E2 in the short postoperative term are beneficial for determining the GCT metastasis.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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