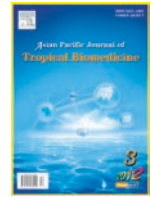




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# Concurrent cystic endometrial hyperplasia, ovarian luteoma and biliary cyst adenoma in an aged rabbit (*Oryctolagus cuniculus*): case report and literature review

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## ABSTRACT

A 6-year-old female nulliparous Dutch Rabbit (*Oryctolagus cuniculus*) was presented in shock status with a history of abdominal distention, inappetance, lethargy, polydipsia, diarrhea and weight loss since 2 weeks ago. There was no breeding history. Radiographic survey showed increased soft tissue opacity dorsal to the urinary bladder and ventral to the colon on the lateral view consistent with uteromegaly and severe intestinal distention resembling intussusceptions. Conservative treatment was failed and the animal died. In necropsy, ileocecal intussusception was noted as the main death factor. Thickened uterine endometrium in both horns was observed and the uterus was filled with mucoid fluid. Both ovaries were multilobulated and distended. On the other hand, a small cyst sized 1.5 × 2.5 cm was diagnosed on the liver surface. Several samples were obtained from lesions for histopathological evaluation. Histopathologically, dilated cystic glands of variable size lined by densely packed epithelium and hyperplasia of the endometrium resulting in irregular folds or papillary projection into the lumen were evident and the sections of ovaries revealed ovarian luteoma that composed of polyhedral cells with pale stained vacuolated cytoplasm, centrally located nuclei with distinct cytoplasmic borders and the cytoplasm of cells contain lipid droplet. The occurrence of biliary cyst adenoma was confirmed by microscopic examination of the mass that composed of multicystic space in different sizes lined by flattened to cuboidal biliary epithelium with papillary projections. These cysts were separated by variable amount of connective tissue. The lack of postmortem investigations in aged rabbits reduced the incidence of neoplastic disease diagnosis in this species. Whereas uterine adenocarcinoma and lymphosarcoma were commonly reported in rabbits, luteoma and biliary cyst adenoma that are well described in this case report were uncommon in rabbit medicine.

## 1. Introduction

The distribution pattern of neoplastic disease in companion animals could be similar with lagomorphs but there are only a few reports in the literature regarding rabbit's tumors. Uterine adenocarcinoma is the most common tumor of intact female rabbits, with incidences of 50–80% in certain breeds over 4 years old. Ageing changes and endometrial hyperplasia often precede adenocarcinoma [1,2,3]. Mammary gland adenocarcinoma is another common neoplastic disease [4]. On the other hand, leiomyoma and leiomyosarcoma of uterine endometrium is another reported tumor of genital system of this species. Hemangioma is the

only reported ovarian tumor in rabbits. Although ovarian tumors are almost common in companion animals such as dogs but luteoma is a rare entity in veterinary medicine [5]. Literature reviews show that Luteoma is the rarest tumor to affect the ovaries and there are limited reports about the occurrence of this tumor in mare, monkey, dog and cat [6–10]. In human medicine, epithelial tumors account for approximately two-thirds of all ovarian tumors whereas 90% of human ovarian cancers are malignant. Sex cord and germ cell tumors account for approximately 6% and 25–30% of all ovarian tumors in human medicine and the frequency of luteoma is lesser than 0.1% [11, 12]. Luteoma, produces progesterone and the occurrence of this tumor in pregnancy was associated with female pseudohermaphroditism [12, 13]. On the other hand, Cystadenoma is a benign tumor, although prone to malignant degeneration, supposedly originating in intrahepatic of biliary epithelium [14, 15]. This kind of

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tumors are rarely diagnosed in pet rabbits, and frequency of reported cases were as two cholangiocarcinomas<sup>[16,17]</sup>, twelve adenomas<sup>[17,18]</sup>, one solitary hamartoma<sup>[19]</sup> and one biliary cystadenoma<sup>[20]</sup> cases. In this clinical report, occurrence of a rare case of benign sex cord–stromal tumor consisted luteoma in both ovaries, cystic endometrial hyperplasia and biliary cyst adenoma was discussed in an aged Dutch rabbit.

## 2. Case report

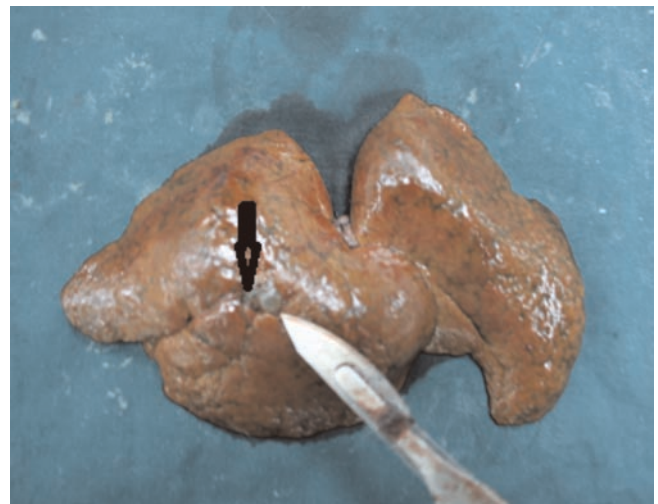
A 6-year-old female nulliparous Dutch Rabbit (*Oryctolagus cuniculus*) was presented with a history of abdominal distention, inappetence, lethargy, polydipsia, diarrhea and weight loss since 2 weeks ago. Dehydration, severe abdominal distension, and mucoid discharge from the external genitalia along with enlarged milk filled teats were observed in clinical examination. Body temperature, pulse rate, and heart rate were considerably decreased and the animal was in shock status. History revealed that the rabbit was not bred so far. Conservative treatment was initiated with intravenous ringer solution and hydrocortisone. Radiographic and laboratory examination revealed leukocytosis and increased soft tissue opacity dorsal to the urinary bladder and ventral to the colon on the lateral view consistent with uteromegaly. Severe intestinal distention resembling intussusceptions. Despite of conservative treatment, the animal was died due to poor clinical condition. At necropsy, ileocecal intussusception was noted as the main death factor. Intussusception caused mesenteric vascular compression and compromise, resulting in venous stasis, hyperaemia and swelling of the affected area developed to coagulative necrosis and death of the animal (Fig 1). Thickened uterine endometrium in both horns was observed and the uterus was filled with mucoid fluid. Both ovaries were multilobulated and distended (Fig 2). On the other hand, a small cyst sized 1.5 × 2.5 cm was diagnosed on the liver surface (Fig 3). Several samples were obtained from lesions for histopathological evaluation. The sections were fixed in buffered 10% formalin, processed in routine manner and embedded in paraffin. Sections (4–5 mm thick) were stained with hematoxylin and eosin stains. Histopathologically dilated cystic glands of variable size lined by densely packed epithelium and hyperplasia of the endometrium resulting in irregular folds or papillar projection into the lumen were evident (Fig 4) and the sections of ovaries revealed ovarian luteoma that composed of multiple lobules of polyhedral cells with pale stained vacuolated cytoplasm, centrally located nuclei with distinct cytoplasmic borders and the cytoplasm of cells contain lipid droplet surrounded by fine connective tissue stroma (Fig 5). The occurrence of biliary cyst adenoma was confirmed by microscopic examination of the mass that composed of multicystic space in different sizes lined by flattened to cuboidal biliary epithelium with papillary projections. These cysts were separated by variable amount of connective tissue (Fig 6).



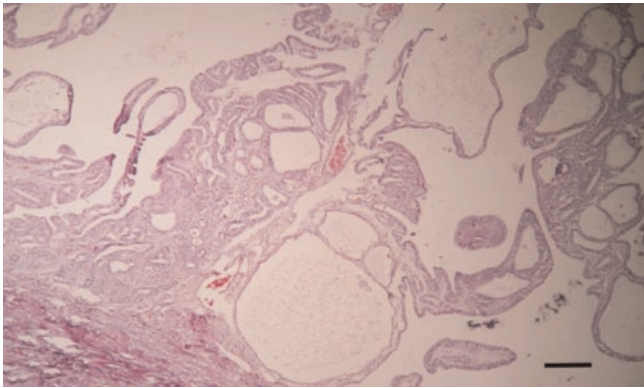
**Fig 1:** Intussusception caused mesenteric vascular compression, hyperaemia and swelling of the affected area developed to coagulative necrosis.



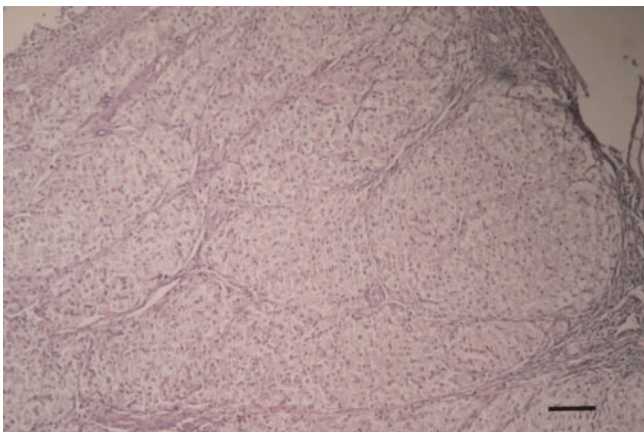
**Fig 2:** Distended and tortuous uterus with numerous cysts varying in size in the endometrium (middle arrow). Both ovaries were multilobulated and distended (black arrows).



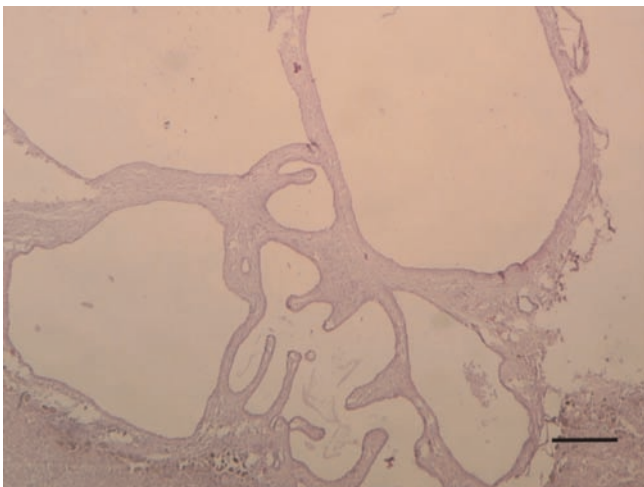
**Fig 3:** Well-circumscribed, rounded cyst on the liver surface.



**Fig 4:** Uterus. Dilated cystic glands of variable size lined by densely packed epithelium and hyperplasia of the endometrium. HE. Bar=250  $\mu$  m



**Fig 5:** Multiple lobules of polyhedral cells with pale stained vacuolated cytoplasm surrounded by fine connective tissue stroma in cystic ovaries. HE. Bar=250  $\mu$  m



**Fig 6:** Biliary cyst adenoma. Multilobular cystic space are lined by flattened epithelium with papillary projection. Bar=250  $\mu$  m

### 3. Discussion

Ovarian tumors are divided into 3 major categories,

which are named according to their presumed histogenesis and differentiation: epithelial tumors, sex cord–stromal tumors, and germ cell tumors [11]. Epithelial tumors include cystadenoma, tubular adenocarcinoma, and mesothelioma. Sex cord–stromal tumors include granulosa cell tumor, luteoma, and thecoma. Germ cell tumor includes dysgerminoma, teratoma, choriocarcinoma, and yolk sac carcinoma [21, 22]. Sex–cord stromal tumors can produce varying amounts of progesterone, estrogen, testosterone, and inhibin, and these hormones can profoundly influence the reproductive behavior of the affected animal and induce changes in extraovarian tissues. With the possible exceptions of the sow and bitch, sex–cord stromal tumors are the most common ovarian neoplasms in domestic species [23]. A small number of malignant mixed mullerian tumors (MMMTs) in cats and rodents have been described [24]. The incidence of ovarian tumors in rabbit varies with the species. Ovarian tumors are more common in older rabbit and are rare before 18 months of age. The rate of tumor growth is variable, and many affected rabbits die of metastatic disease 1–2 years after the onset of clinical signs of disease [17]. A variety of uterine neoplasms including adenocarcinoma may occur in rabbits but the occurrence of ovarian tumors is very rare.

Whereas cystic endometrial hyperplasia (CEH) is a relatively common disease of aged rabbits but ovarian tumors have not been reported as the primary factor to cause it. It seems that in the present case, this phenomenon was due to ovarian luteoma. CEH most often is the result of a heightened sensitivity of the endometrium to stimulation by endogenous progesterone due to retained corpora lutea or ovarian cysts [25]. The histological appearance of CEH induced by progesterone and estrogen is quite different. The epithelium of the endometrium is columnar with extensively vacuolated cytoplasm under progestational influence and cuboidal to low columnar under estrogenic stimulation [23] whereas, the former characteristic changes were evident in the present case.

Biliary cystadenomas are rare, slow growing, multilocular cystic tumors that represent less than 5% of intrahepatic cystic masses of biliary in medicine [26]. The etiology and pathogenesis of biliary adenomas are not fully understood, although several reports suggest that these tumors may originate from reactive proliferation of the biliary epithelium secondary to noxious stimuli, particularly infections [16, 18]. Stimuli such as ischemia or carcinogenic elements also produce this kind of lesions [27]. Due to the absence of clinical symptoms, the diagnosis of biliary adenoma is difficult and most cases were accidentally detected in necropsy. Although this case was too advanced for treatment, when solitary or multiple small tumors are confined to a single liver lobe, surgical excision or lobectomy can be curative [28, 29].

Based on limited current knowledge about neoplastic disease in aged rabbits, reporting of similar cases could be valuable for practitioners who were involved in lagomorphs

medicine.

### Conflict of interest statement

We declare that we have no conflict of interest.

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