

Papillary cystic uterine adenocarcinoma in a New Zealand rabbit: Histopathology of a hidden reproductive threat

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ABSTRACT

A 5-year-old female New Zealand White rabbit weighing 2.4 kg was presented with a history of repeated infertility following three unsuccessful matings and progressive abdominal distension. Owing to chronic infertility and clinical deterioration, the animal was euthanised and subjected to post-mortem examination. Necropsy revealed marked enlargement of both uterine horns and the uterine body with multiple firm, irregular masses and absence of fetuses. Histopathological examination showed an endometrial neoplasm infiltrating the myometrium, composed of papillary, tubular and cystic arrangements of epithelial cells supported by fibrovascular stroma. The neoplastic cells exhibited moderate pleomorphism with low mitotic activity and no metastatic lesions were observed in other organs. Immunohistochemically, the tumor cells showed strong cytoplasmic positivity for cytokeratin-7 and moderate apical to cytoplasmic expression of epithelial membrane antigen. Based on histomorphological features, the tumour was diagnosed as papillary and cystic adenocarcinoma of the uterus.

Key words: Adenocarcinoma, Histopathology, Rabbit, Tumor, Uterus

Rabbit farming focuses on the production and management of domestic rabbits (*Oryctolagus cuniculus*) for meat, fur, wool, research and companion animals. Rabbits are best known for their prolificacy, high fecundity, short generation interval, energy efficiency, and efficient feed conversion, traits that have made them valuable livestock and research subjects worldwide¹. Despite these production advantages, rabbits are susceptible to a wide array of illnesses and reproductive pathologies that can adversely affect health, productivity and welfare². Reproductive disorders further compound health and productivity concerns in female rabbits. Genital infections such as metritis, endometritis and pyometra are common and can lead to infertility or death if untreated; these conditions are frequently observed in commercial and small-scale rabbit operations alike cuniculture. Symptomatic reproductive infections are associated with chronic infertility, inflammation of the reproductive tract and obstetrical complications, thereby reducing reproductive efficiency in doe³.

Uterine neoplasia is a major health concern in female rabbits (*Oryctolagus cuniculus*) with uterine adenocarcinoma being the less common tumour affecting the female reproductive tract. Multiple retrospective studies and clinical reports have documented the high prevalence of this malignancy in intact female rabbits, particularly as animals age. Uterine adenocarcinoma arises from the endometrial epithelium and represents the predominant form of reproductive neoplasia in this species⁴. The high prevalence of neoplasia unique among common domestic species; other animals such as guinea pigs and rodents may develop uterine lesions but tend to have a greater proportion of benign pathology compared to rabbits. In a comparative study of reproductive tract tumours in

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small pet mammals, endometrial adenocarcinoma predominated in rabbits, while benign lesions were more common in species like guinea pigs⁵. Clinically, affected rabbits may present with non-specific signs such as hematuria, serosanguinous vaginal discharge, abdominal distension, anorexia or depression; in many cases, abdominal palpation reveals enlarged or irregular uterine masses⁶. These tumours tend to be slow-growing but locally invasive with metastatic spread commonly occurring within 12 to 24 months after

onset of clinical signs. The lungs are the most frequently reported site of metastasis, followed by liver, bone and other visceral organs⁷. Histologically, adenocarcinomas of the rabbit uterus demonstrate diverse growth patterns, including tubular, solid and papillary variants, the latter characterized by fibrovascular cores lined by neoplastic epithelial cells projecting into glandular lumina⁸ and this report describes a case of uterine papillary cystic adenocarcinoma and also elaborates the histopathology of uterine adenocarcinoma in a New Zealand White rabbit.

A 5-year-old female New Zealand White rabbit weighing 2.4 kg from the Rabbit Breeding Unit at the Post Graduate Research Institute in Animal Sciences (PGRIAS), Kattupakkam showed signs of repeated infertility. The doe had been naturally mated on three separate occasions, each mating occurring at one-month intervals. Pregnancy diagnosis was performed following each mating and all examinations revealed negative results. On the day of clinical presentation, the rabbit was approximately 15 days beyond the expected gestation period. Despite the absence of confirmed pregnancy, the animal exhibited persistent abdominal enlargement. In view of the chronic infertility and progressive abdominal distension, the animal was humanely euthanised following standard ethical procedures.

On necropsy, multiple pale-red hard, sacular masses were observed on both uterine horns (Fig.1) and no fetuses were present in the uterine horns. Representative

tissue samples were collected from different regions of the mass and fixed in 10% neutral buffered formalin for histopathological evaluation. Tissues were processed using the standard paraffin-embedding technique. Sections of 5 μ m thickness were prepared and stained with haematoxylin and eosin (H & E)⁹ for microscopic examination. Immunohistochemical staining for Cytokeratin (CK-7) and epithelial membrane antigen (EMA) was performed as per recommendation of the manufacturer (PathnSitu, USA) using super sensitive labeled poly horse radish peroxidase (HRP) polymer method. Paraffin-embedded uterine tumor tissues sectioned at 3–5 μ m thickness and mounted on poly-L-lysine-coated slides. Sections were dried, deparaffinized in xylene, and rehydrated through graded alcohol to distilled water. Antigen retrieval was performed using heat-induced epitope retrieval (HIER) in citrate buffer (pH 6.0) in a microwave/pressure cooker for 10–20 minutes. Slides were allowed to cool at room temperature. Endogenous peroxidase activity was blocked using 3% hydrogen peroxide for 10 minutes. Non-specific binding was minimized using a protein blocking. Sections were incubated with primary antibodies, CK& and EMA. Incubation was carried out for 1 hour at room temperature. After washing with PBS, slides were treated with HRP-conjugated secondary antibody and visualized using DAB (3,3'-diaminobenzidine) chromogen, producing a brown reaction product. Sections were counterstained with hematoxylin, dehydrated, cleared, and mounted.

Histopathological examination of the tumour

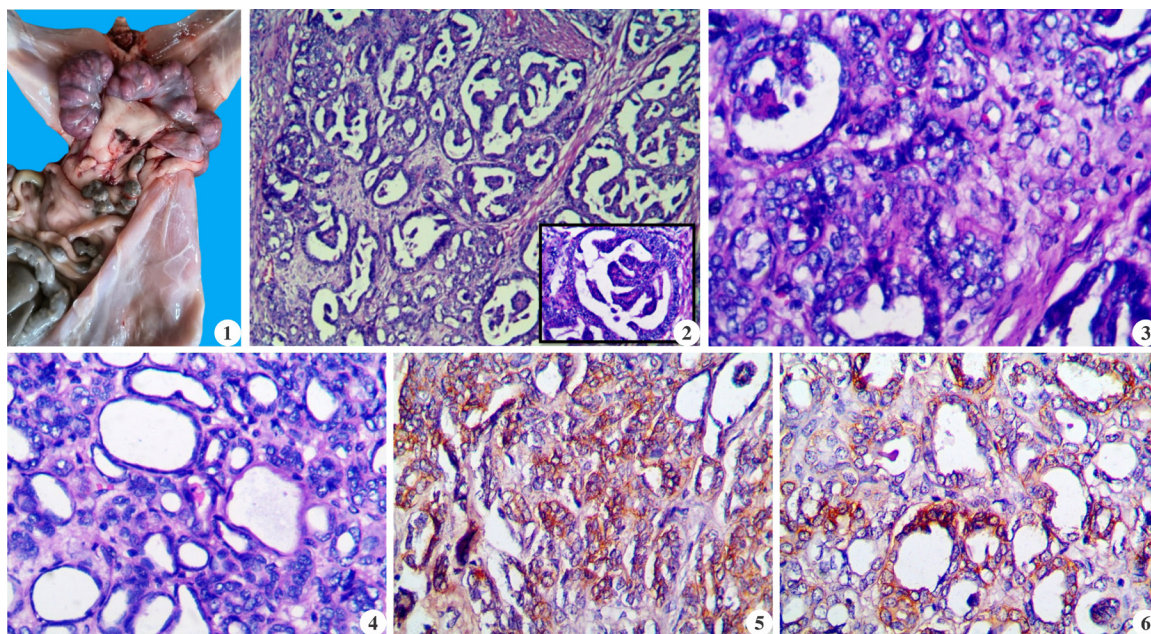


Fig.1. Uterus with multiple hard spherical masses; **Fig. 2.** Uterus: Papillary adenocarcinoma. H&E $\times$ 100. Inset: Papillary projections; **Fig. 3.** Uterus Papillary Adenocarcinoma - Moderate anisocytosis and anisokaryosis. H&E $\times$ 400; **Fig. 4.** Uterus: Papillary cystadenocarcinoma- Multiple thin walled cysts with flattened epithelium. H&E $\times$ 400; **Fig. 5.** Cytokeratin 7 - Strong diffuse cytoplasmic expression. IHC, DAB Brown $\times$ 400; **Fig. 6.** EMA - Moderate expressions of mixed apical and cytoplasmic staining. IHC, DAB Brown $\times$ 400

mass revealed an expansile neoplasm arising from the endometrium with marked infiltration into the underlying myometrium. The neoplastic cells were predominantly arranged in well-defined tubular structures and complex papillary projections, which extended into the uterine lumen (Fig. 2) as well as into the endometrial glandular architecture. These papillary fronds were supported by a delicate fibrovascular stroma imparting a characteristic papillary appearance to the tumour. The neoplasm was composed of polygonal to columnar or cuboidal epithelial cells exhibiting moderate pleomorphism. The cells showed moderate anisocytosis and anisokaryosis (Fig. 3), with hyperchromatic nuclei and indistinct cell borders. Mitotic activity was low to moderate, with one to two mitotic figures. In certain regions, the tumour exhibited moderate to severe cystic degeneration characterized by variably sized cystic spaces lined by flattened to attenuated epithelial cells (Fig. 4). These cystic areas were interspersed within the neoplastic tissue and contributed to the heterogeneous histomorphology of the mass. Microscopic evaluation of the lungs and other major visceral organs did not reveal any evidence of metastatic spread. The neoplastic glandular epithelial cells showed diffuse strong cytoplasmic positivity for CK-7 (Fig. 5) and EMA showed moderate expressions of mixed apical and cytoplasmic staining pattern in moderately differentiated areas (Fig. 6). Based on the histopathological and immunohistochemical features observed, the neoplasm was diagnosed as uterine papillary cystic adenocarcinoma.

Uterine adenocarcinoma is one of the most frequently diagnosed malignancies in domestic rabbits and is widely recognised as uncommon reproductive neoplasm in this species. In contrast to many other domestic mammals where uterine adenocarcinoma is rare, intact female rabbits demonstrate a markedly higher predisposition to this tumour type, particularly as age advances¹⁰. Several retrospective studies have demonstrated that uterine adenocarcinoma is highly prevalent in older rabbits. Large pathological surveys of the genital tract indicate that uterine tumours are the most common uterine disorder in pet rabbits, with adenocarcinoma being the predominant neoplasm⁴. Prospective studies have reported that approximately 40 % of rabbits over three years of age are affected by malignant uterine neoplasia, while clinical case series have documented an incidence ranging from 43 % to more than 50 % among rabbits presented with suspected uterine disease often in association with cystic endometrial hyperplasia². Breed predispositions have been suggested, with New Zealand White, Dutch, and California breeds frequently represented in studies reporting high prevalence, although statistical breed predisposition is variable across datasets^{11,10}.

The exact pathogenesis of uterine adenocarcinoma

in rabbits remains unclear; however, several biological and environmental factors have been proposed. Persistent unopposed estrogen stimulation related to the induced ovulatory nature of rabbits¹² and frequent pseudopregnancies known to be considered as major predisposing factor, promoting prolonged endometrial proliferation and neoplastic transformation. Histological alterations such as endometrial hyperplasia, glandular epithelial atrophy and increased stromal collagen deposition are commonly observed preceding lesions, supporting a progressive transition from hyperplasia to adenocarcinoma¹³. Additionally, immunohistochemical studies have demonstrated overexpression of cyclooxygenase-2 (COX-2) in tumour tissues suggesting its role in tumour development and progression⁸. In the present study, CK7 showed strong diffuse cytoplasmic positivity, consistent with its expression in endometrial glandular epithelium and CK7 is a reliable marker of Müllerian-derived epithelial tumors¹⁴. EMA (MUC1) expression demonstrated a grade-dependent staining pattern, similar observations have been reported in endometrial adenocarcinomas across species¹⁵.

Although inherited susceptibility has been suggested in certain breeds, definitive genetic determinants have not yet been identified. The reproductive history of rabbits with uterine adenocarcinoma frequently reveals disturbances such as diminished fertility, reduced litter size, stillbirths and failed pregnancies preceding tumour detection. The chronic infertility and repeated negative pregnancy diagnoses described in this case align with accounts from clinical studies of reproductive disruption preceding histologically confirmed adenocarcinoma. Uterine adenocarcinoma is an uncommon neoplasm in intact female rabbits, particularly in older does and often manifests as chronic infertility and progressive abdominal distension. Definitive diagnosis relies on histopathological examination, as clinical signs may remain subtle until the disease reaches an advanced stage. In the present case, papillary and cystic adenocarcinoma with myometrial invasion was identified without evidence of metastasis. From a farm management perspective, this condition leads to repeated breeding failures and reduced reproductive efficiency, resulting in increased feed, labour and housing costs. Delayed diagnosis frequently necessitates culling or euthanasia, causing direct economic losses and loss of valuable breeding stock. Therefore, routine reproductive health monitoring, timely culling of affected does and preventive measures such as ovariectomy in non-breeding animals are essential to improve productivity, animal welfare and the economic sustainability of rabbit farming systems.

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