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Metastatic Uterine Adenocarcinoma in an 8-year-old Gilt

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An 8-y-old gilt was evaluated after the onset of hemorrhagic perineal discharge. Uterine adenocarcinoma with metastases to the lungs and regional lymph nodes was diagnosed at necropsy. Tumor cells lacked expression of estrogen receptor α and progesterone receptor. This case represents the first reported uterine adenocarcinoma in a research pig and the first swine uterine neoplasia in which steroid hormone receptor expression was evaluated.

Abbreviations: ERα, estrogen receptor α; PR, progesterone receptor; CEH, cystic endometrial hyperplasia.

Endometrial carcinoma is the most common invasive neoplasm of the human female reproductive tract and accounts for 7% of all invasive cancers in women, excluding skin cancer.[7] Uterine adenocarcinoma is the most common type of tumor in rabbits, often metastasizing to the liver, lungs, and other organs.[5,20] Endometrial carcinoma is uncommon in other domestic animals, but it occurs more frequently in cattle than other species.[19] Few cases of uterine adenocarcinoma in pigs have been reported, possibly because most pigs are slaughtered before they reach an age at which neoplasia is more common.[18] Older female pigs may be subject to development of genital neoplasia because most are not ovariohysterectomized and pet pigs are normally not bred, making female pigs subject to cyclic hormonal influences about every 21 d.[1] To date, only 3 cases of uterine adenocarcinoma in swine have been reported.[13,15,21] The present case is the first report of uterine adenocarcinoma in swine in which steroid sex hormone receptor expression has been evaluated.

Case Report

In December 2007, an 8-y-old, mixed breed (Spotted Poland China × Chapel Hill) research gilt housed in an indoor laboratory animal facility presented with inappetance and a large amount of dried, black discharge on her perineum. No other swine in the AAALAC-accredited facility exhibited similar clinical signs. The gilt was born within the facility and had remained within the closed swine colony. Two attempts had been made to breed this gilt at 2 y of age by using natural hand mating to 2 different boars; both attempts were unsuccessful as determined by abdominal ultrasonography or return to estrus. Further breeding was delayed while new housing facilities were constructed. Consequently this gilt was 6 to 7 y of age when additional unsuccessful attempts at natural mating, including pasture housing for 5 mo with a proven boar, were made. In all instances, the gilt was observed to be in behavioral estrus at the time of breeding. In June 2007, the gilt was enrolled in a atherosclerosis study, which was approved by the University of North Carolina Institutional Animal Care and Use Committee. As part of the study, she was fed a diet consisting of 20% (high) fat and 1% cholesterol diet for 2 mo followed by a 20% fat and 10% sucrose diet for 3 mo. She had just completed the dietary study and was being placed back on a standard pig chow diet at the time the discharge and inappetance were noted.

The swine colony has been serologically and clinically negative for porcine reproductive and respiratory syndrome, *Brucella* spp., and pseudorabies. The herd had shown serologic evidence of a subclinical *Leptospira bratislava* infection in early 2005. Since that time, the colony has been routinely vaccinated with an inactivated vaccine containing *Leptospira bratislava, L. canicola, L. grippotyphosa, L. hardjo, L. icterohaemorrhagiae, L. pomona*, porcine parvovirus, and *Erysipelothrix rhusiopathiae* 2 or 3 times a year.

Physical examination of the gilt at the time the perineal discharge was noted revealed slightly reddened vulvar mucosa with clear discharge. Her bodyweight was 250 kg, which was decreased from 264 kg the previous year. The gilt was bright, alert, and responsive with normal vital signs. A differential diagnoses list included open pyometra or metritis, gastric ulcer, swine dysentery (*Brachyspira hyodysenteriae*), porcine hemorrhagic enteropathy (*Lawsonia intracellularis*), salmonellosis (*Salmonella cholerasuis, S. typhimurium*), and intestinal parasitism (*Trichuris suis*).

Blood drawn for a complete blood count and serum chemistry profile revealed a mild anemia, lymphopenia, monocytosis, eosinophilia, and basophilia (Table 1), making pyometra an unlikely diagnosis. Although blood cholesterol was 190 mg/dL (reference range, 36 to 54 mg/dL), the pig had just finished a dietary study in which she was fed a high-fat diet; otherwise, serum chemistry values were unremarkable. Direct fecal examination and fecal flotation for common swine intestinal parasites were negative. A vaginal swab taken by using a sterile cotton-tip applicator and nonsterile speculum grew β-hemolytic group C *Streptococcus equisimilis*, coagulase-positive *Staphylococcus* spp., and a few nonhemolytic *Escherichia coli*. *S. equisimilis* is considered a commensal organism in swine vaginal secretions.[12] The gilt received oxytetracycline (10 mg/kg once daily) in her feed for 1 wk pending results of vaginal bacterial culture and sensitivity testing. Because gastric ulceration had been a problem in other swine on high-fat diets, she also received oral omeprazole (0.4 mg/kg once daily) and sucralfate (3 g twice daily) as a gastric protectant.

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Table 1. Hematology values

	12/4/2007	12/10/2007	Reference range[a]
RBC	5.87 x 10^6	5.66 x 10^6	6.1-7.9 x 10^6/μL
WBC	21,700	25,200	11,200–22,000/μL
Neutrophils	13,800 (64%)	14,600 (58%)	19% to 60%
Bands	0	756 (3%)	0% to 1%
Lymphocytes	3,906 (18%)	6,000 (24%)	40% to 75%
Monocytes	1,953 (9%)	1,500 (6%)	0% to 2%
Eosinophils	1,085 (5%)	1,500 (6%)	0% to 4%
Basophils	868 (4%)	750 (3%)	0%

[a]As reported by Antech Diagnostics (Lake Success, NY).

After 1 wk of treatment, on follow-up examination, the gilt was bright, alert, and responsive and had no evidence of perineal discharge. Her feces were dry and normal in color, but she continued to have a decreased appetite. At this time, repeat hematology showed continued anemia, leukocytosis with a regenerative left shift, lymphopenia, monocytosis, eosinophilia, and basophilia (Table 1). In light of the antibiotic sensitivity results, oxytetracycline was discontinued at this time, and treatment with enrofloxacin (5 mg/kg PO once daily) was initiated. Three days later, the investigator elected to euthanize the gilt because she continued to have persistent leukocytosis and a decreased appetite and was no longer a research candidate.

On necropsy, significant gross lesions were limited to the urogenital tract, abdominal cavity, abdominal lymph nodes, and lungs. The uterus was diffusely enlarged, and a firm, cream-colored mass measuring approximately 12 cm × 7 cm × 8 cm was present within the right uterine horn wall (Figure 1). The uterine horns were opened, and the endometrium was diffusely reddened and had variably sized cysts filled with clear fluid throughout the mucosa. An oblong, cream-colored mass measuring 3 cm × 2 cm × 1 cm was located in the left uterine broad ligament (Figure 1, arrow). Both ovaries contained multiple clear to hemorrhagic cysts measuring as large as 2 cm (Figure 1, arrowheads). A firm, cream-colored mass measuring approximately 15 cm × 10 cm × 7 cm with a necrotic center was located within the abdomen in the region of, and replacing, the right medial iliac lymph nodes. Lymph nodes along the descending aorta were markedly enlarged, firm, and cream-colored. The lungs had multiple, firm, cream-colored masses that varied from less than 0.5 cm to approximately 2 cm in diameter distributed throughout the parenchyma (Figure 2).

Tissue samples were immersion-fixed in 10% neutral buffered formalin for histology. On histologic examination of sections stained with hematoxylin and eosin, the endometrium within the uterine mass was effaced by branching cords of anaplastic epithelial cells with large reticulated nuclei, multiple prominent nucleoli, moderate eosinophilic cytoplasm, and indistinct cell borders (Figure 3). These endometrial tumor cells formed few distorted glands, mitotic figures were common (6 to 8 per 40× field), and there was considerable tumor necrosis. When invading the underlying myometrium, the neoplastic cells formed more distinct glands lined by crowded tall columnar cells (Figure 3). The uterine neoplastic cells were surrounded by variable amounts of scirrhous connective tissue infiltrated by abundant mononuclear inflammatory cells and eosinophils. There was no evidence of squamous differentiation or chondroid metaplasia in examined sections of the uterine mass. Other sections of uterine endometrium contained normal glandular structures admixed with large cystic glands lined by low cuboidal to crowded tall columnar epithelium. Pulmonary

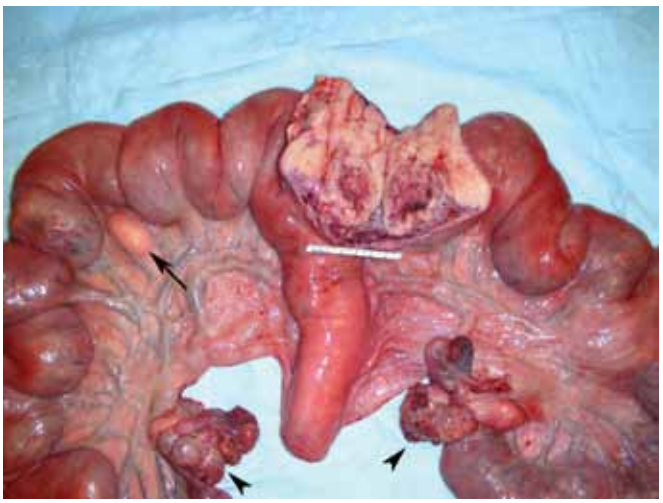

Figure 1. The uterus was diffusely enlarged with thick polycystic walls and dark fluid contents. A large mass was present within the right uterine horn near the uterine bifurcation. On cut section, this mass was firm and cream-colored with a necrotic center. The broad ligament of the left uterine horn contained a similar oblong, cream-colored mass (arrow). Both ovaries (arrowheads) exhibited multiple, variably sized cysts.

nodules consisted of neoplastic cords and glands, similar to those observed in the uterine mass, and surrounded by variable amounts of scirrhous connective tissue containing lymphocytes and eosinophils. Microscopically, additional clusters of neoplastic cells were located within alveoli (Figure 4). There was moderate multifocal pulmonary edema. Lymph nodes adjacent to the abdominal aorta, as well as the mass replacing the right medial iliac lymph nodes, also contained similar scirrhous and neoplastic lesions.

An immunohistochemical analysis of the uterine tissue was conducted by using antibodies to estrogen receptor α (ERα; Beckman Coulter, Fullerton, CA) and progesterone receptor (PR; Beckman Coulter) antibodies. Tissues were deparaffinized in xylene and rehydrated through graded ethanol. Endogenous peroxidase was blocked by using 3% H_2O_2, followed by epitope retrieval in 6.0 M sodium citrate buffer in a pressure cooker, which involved decloaking for 5 min until the temperature reached 120 °C, holding for 5 min at 19 lb/in.^{2} at 120 °C, and then depressurizing over 10 min. The Vectastain Mouse Elite Kit (Vector Laboratories, Burlingame, CA) was used as the detection system. Antibodies were applied at 1:600 for PR and 1:300 for ERα and incubated for 1 h at room temperature. Staining was visualized by using 3-diaminobenzidine chromagen (DakoCytomation, Carpenteria, CA) and Harris hematoxylin counterstain. All sections were dehydrated through graded

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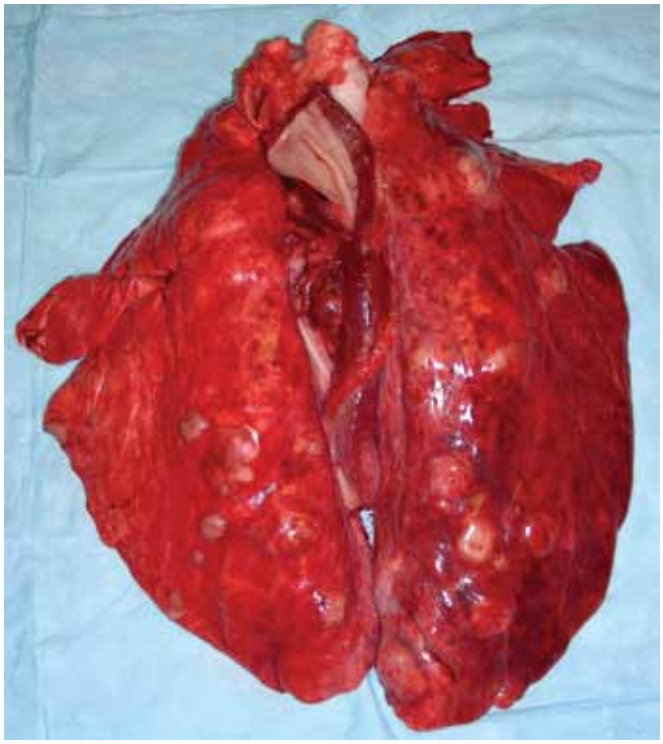

Figure 2. The gilt's lungs had multiple, firm, cream-colored masses scattered throughout the parenchyma.

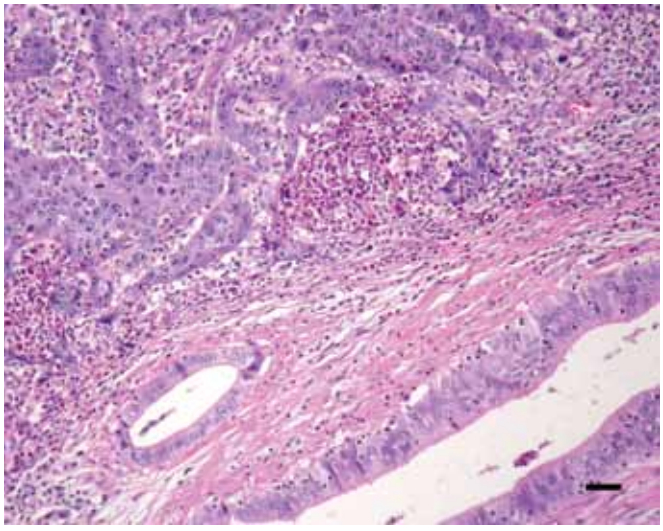

Figure 3. The endometrium in the uterine mass was effaced by cords of dysplastic epithelial cells with large nuclei, prominent nucleoli, and reticulated chromatin patterns (upper left). Areas of tumor necrosis and stromal inflammation were visible. When invading the myometrium, tumor cells tended to form more discrete glands (lower right). Scale bar, 60 µm.

ethanol, cleared in xylene, and coverslipped. For negative controls, a nonimmune mouse serum was used in place of the antibody. Sections of uterine tumor mass and areas of cystic endometrial hyperplasia from this gilt, as well as normal uterine tissue from a different pig representing normal swine uterus, were evaluated. Surface epithelial and glandular epithelial and myometrial nuclei were all positive for both ERα and PR in both normal uterus and areas of cystic endometrial hyperplasia (Figures 5 and 6). Uterine tumor cells were uniformly negative for ERα (Figure 5), and fewer than 10% of tumor nuclei had faint, granular staining for PR (Figure 6). In

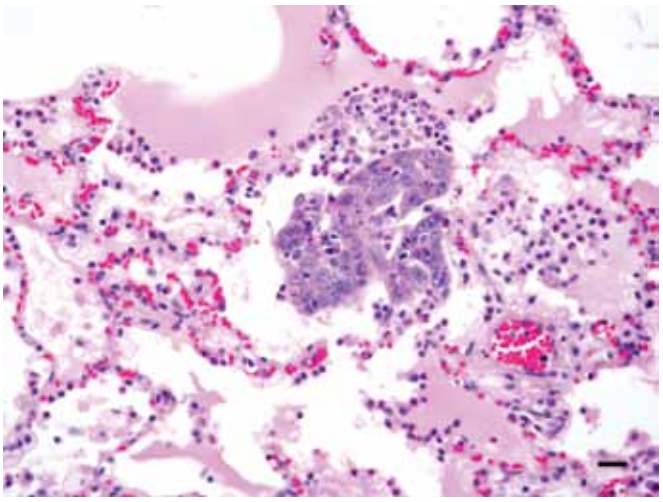

Figure 4. Metastatic tumor in the lung with associated inflammation and edema. Scale bar, 60 µm.

light of the clinical history and gross and histopathologic lesions, diagnoses of cystic endometrial hyperplasia, cystic ovaries, and uterine adenocarcinoma with pulmonary and lymph node metastases were made.

Discussion

To date, 3 cases of uterine adenocarcinoma in different breeds of swine have been reported.[13,15,21] The current case is the first report of uterine adenocarcinoma in a pig in a research environment. This 8-y-old crossbred Spotted Poland × Chapel Hill gilt had no history of pregnancy. The uterine adenocarcinoma had metastasized to the lungs and abdominal lymph nodes and was associated with cystic uterine endometrial hyperplasia. In 1900, an adenocarcinoma in a sow of unknown breed was reported to have metastasized to the sublumbar lymph nodes.[15] This tumor was described as having foci of well-preserved glandular structures as well as continuous rows of cells surrounded by a fibromyxomatous stroma. Cystic endometrial hyperplasia was not reported and no age or reproductive history was described for that animal.[15] The uterine adenocarcinoma in a 3-y-old crossbred Chester White–Hampshire–Duroc sow consisted of islands of closely packed neoplastic epithelial cells, most forming distinct acini with numerous mitotic figures surrounded by a proliferative fibrous stroma.[21] In contrast to our report, no tumor metastases were identified. The sow had farrowed 3 normal litters and had no history of infertility or clinical evidence of hyperestrogenism, such as cystic endometrial hyperplasia.[21] A case of diffuse cystic endometrial hyperplasia and metastatic endometrial adenocarcinoma in a 16-y-old Vietnamese pot-bellied pig has been reported.[13] Glandular elements were identified in the neoplastic foci, and mitoses were numerous. Metastatic foci were found in the liver as well as lung, medial iliac, lumbar aortic and thoracic aortic lymph nodes. Similar to our findings, cells in the metastatic foci were more pleomorphic than those in the primary tumor. Clinical similarities included inappetance and weight loss; however, there were no reproductive records to indicate whether the reported pig had exhibited normal reproductive cycles or had farrowed.[13] In addition, the pig breed and environmental setting were different from those of the current case report.

In general, additional reports of other types of female swine genital neoplasia are sparse. Among farm animals in a British abattoir where 3.7 million pigs between the ages of 6 mo and 5 y

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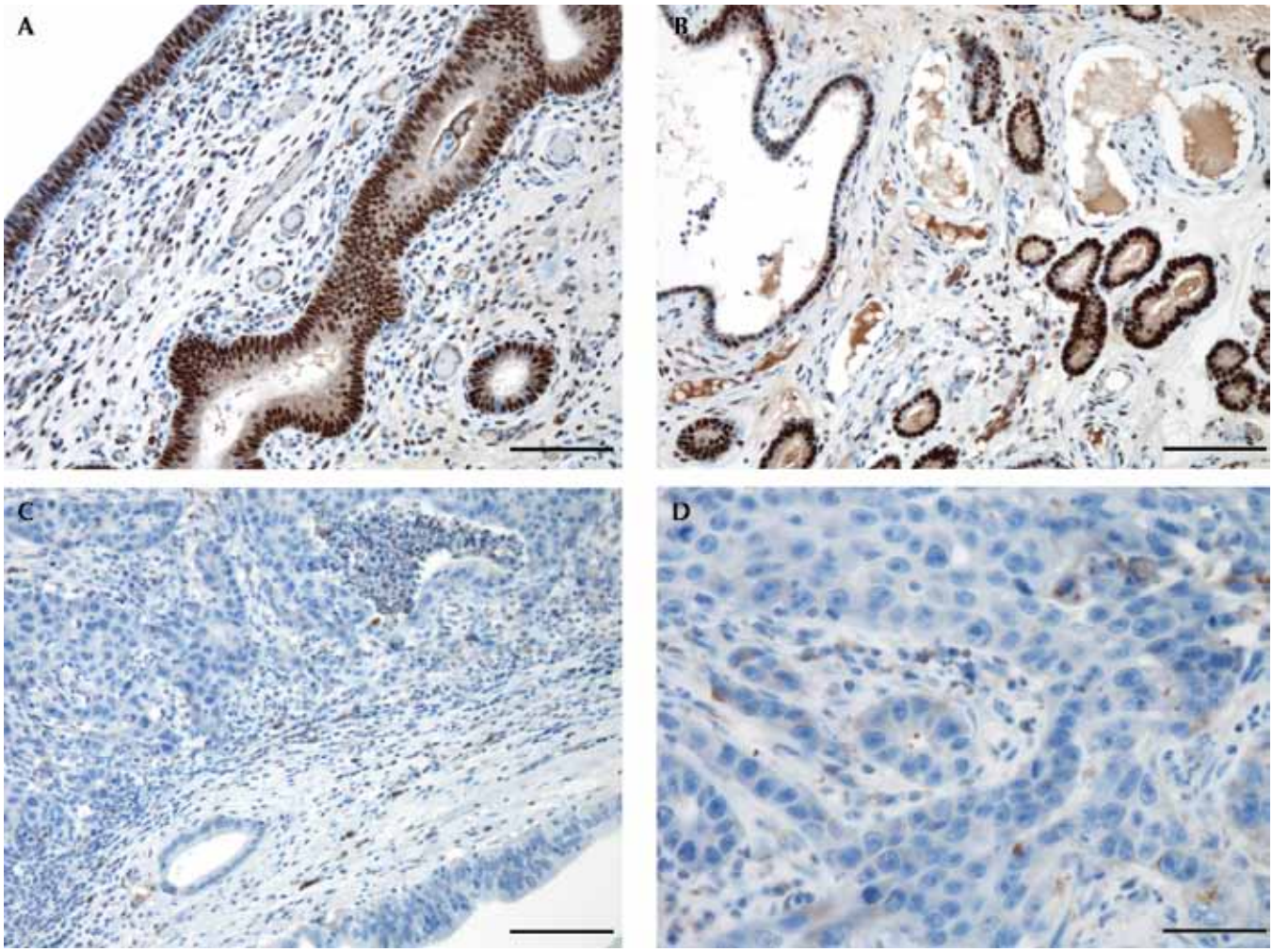

Figure 5. Immunostaining of ERα in (A) a normal pig uterus compared with areas of (B) cystic endometrial hyperplasia and (C, D) endometrial adenocarcinoma in the pig presented. There is strong diffuse nuclear staining in endometrial glands in both (A) normal uterus and (B) endometrial hyperplasia. Staining of the surface epithelium and endometrial stroma in panels A and B is intermittent and of variable intensity. ERα staining is (C) completely absent in the endometrial adenocarcinoma and (D) greatly reduced in adjacent endometrial stroma. Scale bar, 100 µm (A–C), 50 µm (D).

were necropsied, genital neoplasia was identified in 6 (4%) of the 139 tumors identified.[3] The tumor types included 1 uterine leiomyosarcoma, 1 uterine adenomyoma, 1 ovarian leiomyoma, 1 granulosa-cell tumor with metastasis, and 2 papillary serous cystadenocarcinomas with metastasis to the lungs. The cited report[3] demonstrates the rarity of endometrial carcinomas in swine. Another report[8] describes 31 spontaneous neoplasms in pigs necropsied at the Animal Disease Diagnostic Laboratory at Purdue University during an 11-y period. The most common neoplasm was lymphosarcoma followed by melanoma. None of the reported neoplasms involved the female genitalia or were classified as carcinomas. A retrospective study identified uterine neoplasia in 13 of 106 female potbellied pigs.[17] Uterine leiomyoma was the most commonly diagnosed (11 of the 13 cases), with 1 leiomyosarcoma and 1 undifferentiated sarcoma in the remaining 2 animals. Other authors reported neoplastic tumors of the genital tract in 68 of 1445 (4.6%) sows from 22 different farms.[2] Uterine tumors consisted of leiomyoma ($n = 6$), fibroma ($n = 3$), cystadenoma ($n = 1$), fibroleiomyoma ($n = 1$), and vaginal tumor ($n = 1$). The remaining 56 of the 68 genital tumors were ovarian tumors. A 10-y-old Landrace sow that had a 2-wk history of chronic weight loss and inappetance was diagnosed with endometrial carcinosarcoma.[6] These reports demonstrate the overall low incidence of reported swine genital tumors and the lower incidence of reported uterine adenocarcinoma.

In contrast, endometrial carcinoma is the most common invasive neoplasm of the human female reproductive tract. Chronic estrogenic stimulation has been associated with endometrial hyperplasia and carcinoma in women, and endometrial carcinoma tends to be most common in aging, nulliparous females with a history of menstrual irregularity consistent with anovulatory cycling.[7] Low parity and later menopause are additional known risk factors for endometrial cancer in women.[4] In studies evaluating ERα in human endometrial carcinomas, ERα-positive tumors had a better prognosis for treatment;[10] however, even well-differentiated adenocarcinomas had a significant decrease in ERα expression compared with age-matched controls.[14] Expression of PR was decreased in postmenopausal endometrium and even further decreased in poorly differentiated endometrial cancers.[14] In contrast, a review of human leiomyoma etiology and pathogenesis revealed that the majority of studies reviewed reported higher concentrations of both ER and PR in leiomyomas than in the normal myometrium.[9]

Rabbits and cats are both induced ovulators that, in the absence of breeding, undergo anovulatory cycling and prolonged estrogenic stimulation of uterine tissues. Recent studies in these species have evaluated the expression of ERα and PR.[11,16] In

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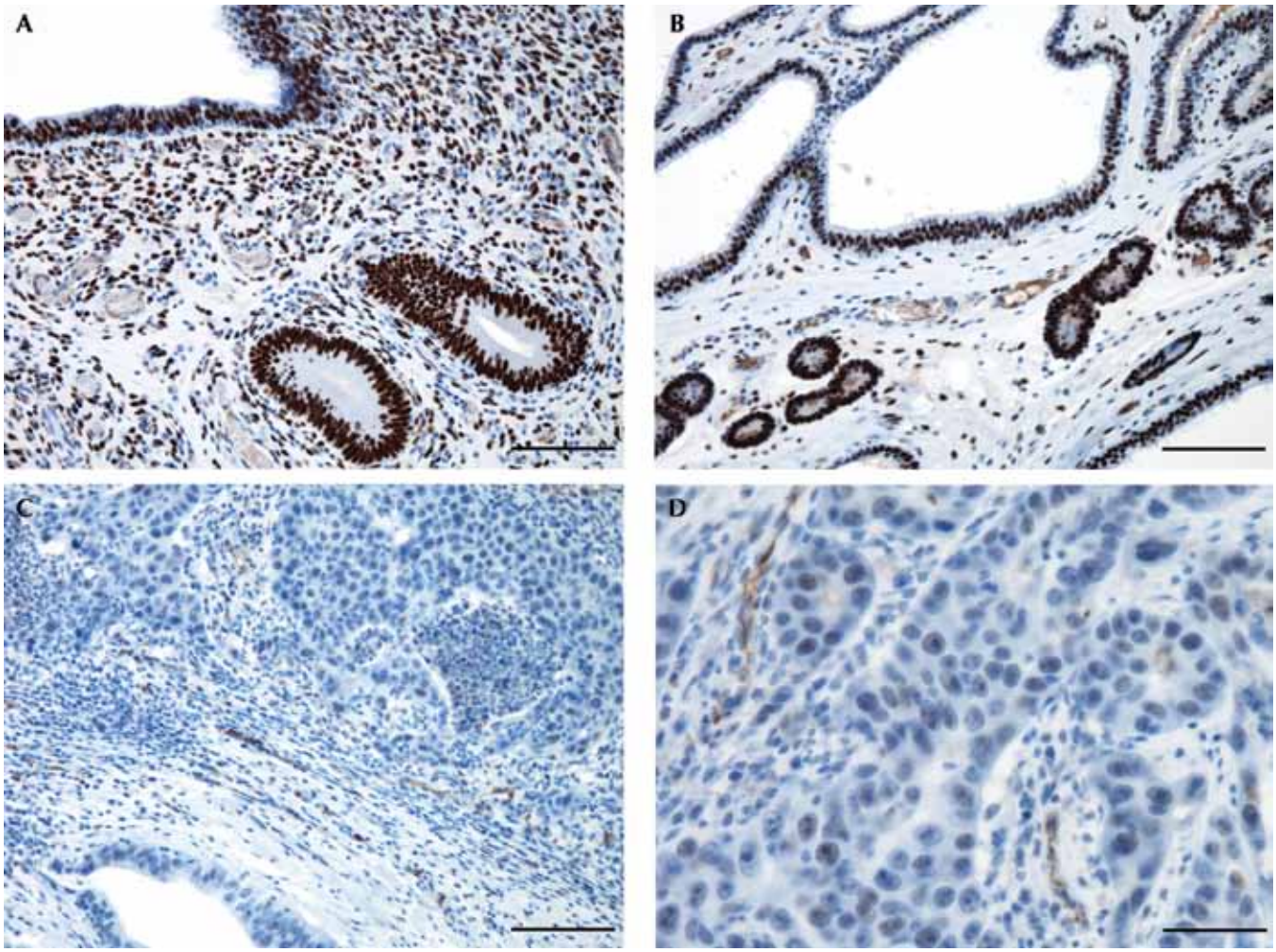

Figure 6. Immunodetection of PR in (A) a normal pig uterus and (B) areas of cystic endometrial hyperplasia and (C, D) endometrial adenocarcinoma in the pig presented. There is strong diffuse nuclear staining in epithelium and endometrial stroma in both (A) normal uterus and (B) cystic endometrial hyperplasia. (C) Faint granular nuclear staining is present in some endometrial carcinoma cells (fewer than 10%), but (D) PR staining is absent in the residual endometrial stroma. Scale bar, 100 µm (A–C), 50 µm (D).

8 cats with uterine adenocarcinoma, marked nuclear atypia and metastases were associated with lack of ERα expression,[16] whereas in another study[11] of 8 different feline tumors, only 1 displayed any expression of ERα, and that was very limited. Other authors that evaluated PR expression[11] reported that expression was reduced markedly in 5 of 6 tumors compared with histologically normal uterine tissues. Rabbits appear to demonstrate 2 different patterns of progression to uterine adenocarcinoma, the first consisting of proliferation of small acini that replace the uterine stroma, and a second, more common pattern of papillary endometrial glandular proliferation.[5] Papillary adenocarcinomas in rabbits are negative for ERα and PR, whereas tubular or solid adenocarcinomas were predominately ERα- and PR-positive;[5] the authors reported no correlation between prognosis and expression of ERα or PR. Ours is the first report in which ERα and PR have been evaluated in swine uterine adenocarcinoma. This animal showed essentially no expression of ERα or PR in neoplastic cells, although other sections of uterus with cystic hyperplasia in the affected animal as well as another normal pig uterus showed expression of both of these steroid hormone receptors. This pig was observed on several occasions to be in behavioral estrus but was unable to conceive, a pattern consistent with anovulatory cycling. Anovulation likely promoted endometrial hyperplasia and subsequent cancer development. The absence of estrogen and progesterone receptors in the tumor is consistent with the invasiveness, marked cellular atypia, and metastases observed in other species.

This case study and the cited reports suggest that aging, nulliparous female swine may be predisposed to uterine lesions that may manifest as neoplasia, similar to those reported in women.[7] With the advent of long-term research studies using swine models of chronic human diseases such as diabetes and atherosclerosis, as well as the development of transgenic lines of swine that may be kept and bred for long periods of time, the incidence of recognized reproductive abnormalities and uterine neoplasia in research pigs may increase.

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