

Seminal Vesicle Carcinoma-In-Situ in An Adult Rhesus Macaque: A Case Report and Review of The Literature

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Abstract

A seminal vesicle carcinoma-in-situ was diagnosed as an incidental finding during histopathological evaluation of necropsy tissues in a 9 year old intact male Indian origin Rhesus macaque. The animal had been used in a series of infectious disease studies and in a terminal renal transplantation experiment over the course of its life at the Armed Forces Research Institute of Medical Sciences. Diagnosis was proffered by a board certified (ACVP) veterinary pathologist due to the microscopic appearance of the neoplasm and confirmed using immunohistochemistry. This report represents the first description of a seminal vesicle carcinoma-in-situ in a non-human primate.

Keywords: adenocarcinoma, histopathology, malignant, rhesus macaque, seminal vesicle

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Introduction

During histopathological evaluation of the tissues of a 9 year old intact male Indian origin rhesus macaque (*Macacca mulatta*) submitted as part of a renal transplantation study, a seminal vesicle carcinoma-in-situ was diagnosed. Due in part to the small size of the tumor and the presence of abundant adhesions and necrosis related to the experimental procedure, the neoplasm within the seminal vesicle was not observed grossly. Microscopic examination of the accessory sex glands noted multiple 1-2mm foci of dysplastic or neoplastic tissue replacing and effacing the normal seminal vesicular architecture within multiple lobules of the organ. Within areas of neoplastic transformation there was abundant desmoplasia associated with abortive neoplastic glands and small islands. In no instance within multiple examined sections of the seminal vesicle had the neoplasm broken through the basement membrane and there was no evidence of metastatic activity in any organ system within the animal.

There are vanishingly rare reports of accessory sex gland tumors in non-human primates with few descriptions of single cases of benign prostatic adenomas in the baboon (Lapin, 1982), mongoose lemur and ring-tailed lemur (Remick et al., 2009) and case reports of malignant prostatic tumors described in the rhesus macaque (Hubbard et al., 1985) and the slow loris (Remick et al., 2009). Tumors of the seminal vesicle are reported only twice in non-human primates. These reports consist of a benign adenoma in a cynomolgus macaque (Kaspereit et al., 2007) and a papillary adenocarcinoma in a Coquerel's giant mouse lemur (Remick et al., 2009).

This is the first report of a seminal vesicle adenocarcinoma-in-situ in a non-human primate and with the exclusion of humans, is the first report of a seminal vesicle malignancy in the primate clade of haplorhini.

Materials and Methods

Case history: The animal is 9 years old, 8.5 kg, male, USAMC-AFRIMS colony born Indian rhesus monkeys. Full compliance with the 8th edition of the, *Guide for the Care and Use of Laboratory Animals* governed all animal care and use. All animal care and procedures were approved by the AFRIMS Animal Care and Use Committee (IACUC).

Commercially available monkey feed produced by a local feed company, was provided to the animal twice daily. The animal received enrichment through a process of rotational toys and food supplementation such as mixed fresh vegetables or seasonal fruits that were provided to the animal four times per week. The chlorinated water was provided to the animal *ad libitum* via automatic watering valves. The monkey was clinically observed 3 times daily by trained animal technicians. Semi-annual physical examinations were performed twice yearly and there was no enlargement or swollen at testis or perineum detected at any point in the animal's history. His annual serology test results were consistently negative for Herpes simian B virus, Simian retrovirus (SRV),

Simian immunodeficiency virus (SIV) and Simian T-cell leukemia virus (STLV-1) since 2004. The animal was employed as a research for malarial drug efficacy test in 2006, a Dengue vaccine efficacy study in 2009 and a terminal renal transplantation protocol in 2012.

Within the scope of the final renal transplantation study, the macaque was utilized on the experimental arm of the study which tested a novel preservative for organ transplantation. Unilateral nephrectomy was performed and then the nephrectomized kidney was preserved and stored in the novel preservative as the static diffusion at room temperature for 24 hours. The subsequent day, the preserved kidney was transplanted back into the animal and the animal was continuously observed its clinical signs for 21 days before euthanasia.

At day 1 after transplantation, the animal was anesthetized for physical examination. It was noted to be depressed, anorexic, to be lame on both hind limbs and to have marked edema in the extremities of both arms, feet, as well as the perineum, prepuce and scrotal sac. Hematology revealed a normocytic normochromic regenerative anemia, a low red blood cell count ($2.19 \times 10^6/\mu\text{l}$) with a hematocrit of 16.6% and a decreased hemoglobin (5.2 gm%). Both the MCV and MCHC were within the normal range. BUN (39.3 mg/dl) and creatinine (4.25 mg/dl) were higher than normal. Anemia was corrected by transfusion blood from the compatible donor monkey. The animal's clinical signs gradually improved and 1 day after receiving the blood transfusion the animal expressed normal activities, was alert and active. Before euthanasia at study day 21, the animal was re-examined and still observed to have an enlargement within the right spermatic cord and right testes.

A complete necropsy was performed immediately following euthanasia and all body systems sampled for histopathological analysis by a board certified veterinary pathologist. Slide preparation was conducted following conventional methodology consisting of processing and embedding tissues in paraffin blocks. Blocks were sectioned at 4 μm and stained with hematoxylin and eosin (H&E). All tissues were evaluated by light microscopy. Immunohistochemistry was performed on samples of the tumor to evaluate immunoreactivity to Vimentin, Cytokeratin-7 and 20, Prostate Specific Acid Phosphatase (PSAP) and Cancer Antigen 125 (CA-125) antigens using published methodology associated with the use of commercially available DAKO kits.

Results and Discussion

Necropsy results: The only external signs noted in the animal at the time of euthanasia were associated with the healing surgical site and an area of chronic swelling on the left hindleg. Exposure of the left fibula noted a region of callous within the midshaft interpreted to be an old traumatic wound. On exploration of the abdominal cavity, the omentum was noted to be multifocally adhered to the abdominal wall as well as the jejunum, colon, urinary bladder and the transplanted kidney. The lymph node adjacent to the transplanted kidney was markedly enlarged and

congested. No additional significant lesions were noted in any organ system within the animal.

Histopathological results: Effacing and replacing the seminal vesicle but constrained within the basement membrane was an unencapsulated invasive neoplasm composed of islands and trabeculae of polygonal cells which occasionally formed abortive glands or tubules. Neoplastic cells had variably distinct cell borders separated by either a fine fibrovascular stroma or by dense streams of fibrous connective tissue (desmoplasia). (Fig 1) Neoplastic cells had a moderate amount of eosinophilic microvacuolated cytoplasm, round to oval vesiculate nuclei with 1 to 2 distinct magenta nucleoli. There was marked anisocytosis and anisokaryosis and the mitotic rate was approximately 1 per high powered field with regional variability (Fig 2). There was frequent single cell necrosis and scattered aggregates of lymphocytes. Within adjacent glandular tissue there was disruption of the normal architecture by epithelial hyperplasia and dysplasia characterized by piling of cells, partial loss of orientation and the presence of significant nuclear pleomorphism. Multifocally seminal glands were expanded by small intraluminal mineral concretions or by few microabscesses. While there was no evidence of metastasis within any examined tissue, histopathological examination of the testes noted mild to moderate germ cell atrophy and frequent intraluminal seminiferous tubular giant cell formation suggestive of degeneration of sperm cells (Fig 3). Concurrent but unrelated histopathological changes in the animal included coagulative necrosis of the transplanted kidney, multifocal, mild accumulations of a crystalline birefringent material within the inguinal lymph node which elicited a mild granulomatous foreign body reaction and the skeletal muscle surrounding the left sciatic nerve was infiltrated by abundant hemosiderosis suggestive of prior hemorrhage, potentially associated with a chronic traumatic lesion. Based on the restriction of the tumor to the vesicle itself, without breaching the basement membrane, the marked cellular atypia and the abundant desmoplasia, we proffered a diagnosis of carcinoma-in-situ of the seminal vesicle.

Immunohistochemical results: Immunohistochemical examination of the neoplastic tissue observed moderate superficial immunoreactivity to Cancer Antigen 125 (Fig 4) as well as strong immunoreactivity to Cytokeratin 7 within the cytoplasm of the neoplastic epithelium (Fig 5). Strong positivity to vimentin was observed in the interstitial and desmoplastic tissues as well as in macrophages admixed within the neoplasm. Cytokeratin 20 and Prostate Specific Acid Phosphatase (PSAP) were negative.

These findings strongly correlate to similar immunohistochemical studies that have been conducted in humans (Ormsby et al., 2000; Thiel and Effert, 2002).

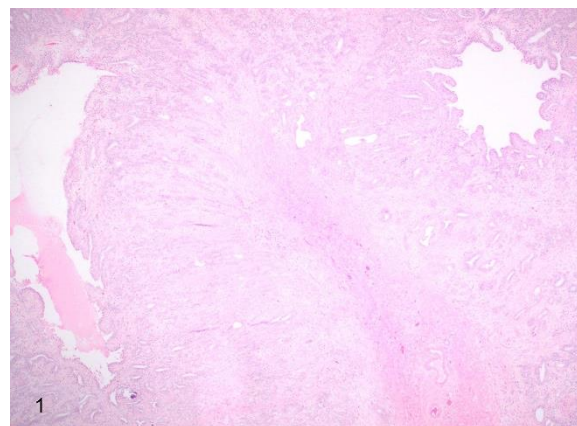


Figure 1 Seminal vesicle: The neoplasm is composed of irregular glands separated by either fine fibrous connective tissue or dense streams of desmoplastic tissue. These are restricted to the architecture of the gland and do not breach the basement membrane. HE stain, 40x

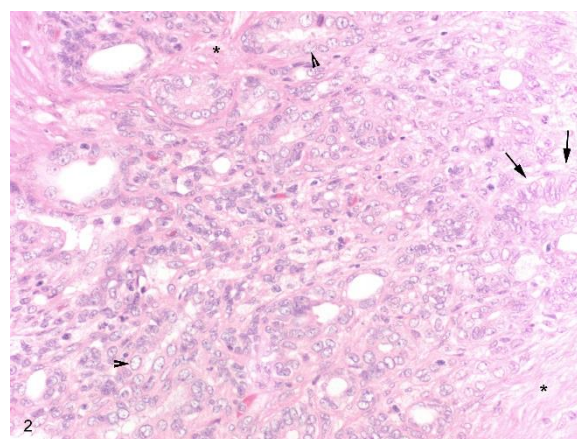


Figure 2 Seminal vesicle: Neoplastic cells have marked pleomorphism (arrowheads) and form abortive glands (arrows) which are separated and surrounded by dense streams of fibrovascular tissue (asterisk) interpreted as a desmoplastic response. HE stain, 400x

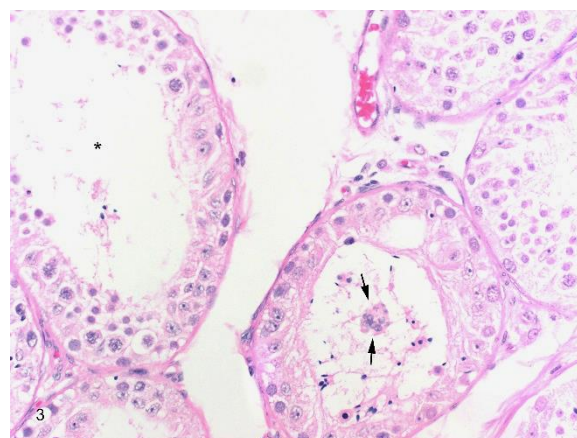


Figure 3 Testis: Multifocally throughout the testis, there is atrophy and loss of mature sperm (asterisk) with degeneration of the germ cells and intraluminal giant cell formation (arrows). HE stain, 400x

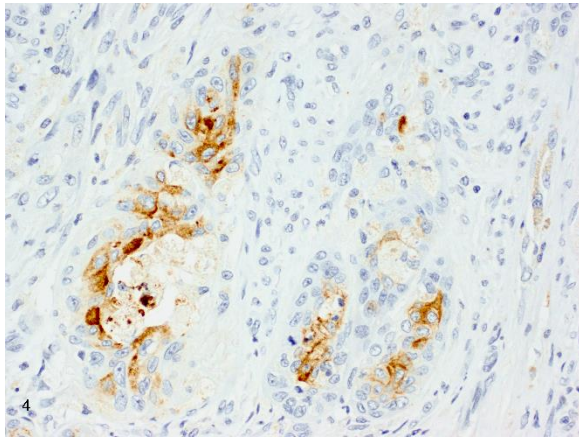


Figure 4 Seminal vesicle: Multifocally the neoplastic epithelium is immunoreactive to CA-125. CA-125 IHC, counterstained with Meyer's hematoxylin, 400x

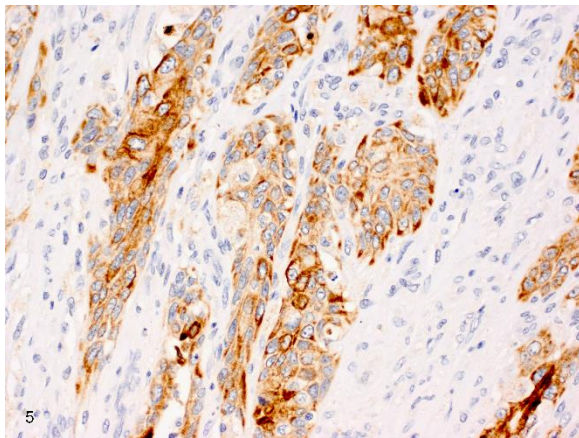


Figure 5 Seminal vesicle: Multifocally the neoplastic epithelium is immunoreactive to CK-7. CK-7 IHC, counterstained with Meyer's hematoxylin, 400x

There is significant interest in the invasion of prostatic tumors into the other accessory sex glands in the medical literature (Epstein et al., 1993) due to the high prevalence in humans and the veterinary literature contains reports of the same, because of the potential for a laboratory species to act as an experimental model for prostate carcinogenesis. (Tani et al., 2005) However, with the exception of carcinogen induced tumors in genetically modified mice and spontaneous tumors in select laboratory rodents, the veterinary literature contains few reports of seminal vesicle malignancies. Retrospective studies of spontaneous lesions in rodents range in incidence rates from one in which over 50,000 male Fischer 344 (F344) rats used in a variety of toxicology and carcinogenicity studies were described with an incidence rate of 0.0004% of benign seminal vesicle neoplasms and no malignant tumors. (Shoda et al., 1998) In contrast to which, another report in a population of aged Han:Chin hamsters recorded a case incidence of 6% out of 182 animals consisting of 5 adenocarcinomas and one hemangiosarcoma. (Kaspereit-Rittinghausen et al., 1988). Apart from these sparse reports in laboratory animals and a single case report in a non-human primate, the literature contains no reports of seminal

vesicle malignancies in other veterinary species. This is in part due to the anatomical absence of the structure in carnivores, monotremes, marsupials and cetaceans, however even in those species which do have seminal vesicles such as pigs and horses, there are no reports of neoplastic transformation in any other species.

The report of the papillary adenocarcinoma in the Coquerel's giant mouse lemur does not include a detailed description of the tumor beyond the presence of papillary projections lined by neoplastic cells, concurrent hemorrhage and necrosis. However cases of seminal vesicle adenocarcinoma in humans are described as a range of well-differentiated papillary carcinomas forming irregular trabeculae and fronds of neoplastic cells supported by a fibrovascular stroma to poorly-differentiated tumors with increased degrees of cellular and nuclear atypia, desmoplasia and necrosis. Carcinoma-in-situ is described in the prostate as part of the continuum of intraductal dysplasia and extending to invasive adenocarcinoma. (Epstein, 1992) In the seminal vesicles, there are several reports of transitional cell carcinomas-in-situ extending from the urinary bladder and involving the urethra, distal ureter and the seminal vesicle, (Jakse et al., 1987) but in a thorough search of both the veterinary and medical literature, we were unable to uncover any reports of a primary carcinoma-in-situ of the seminal vesicle.

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บทคัดย่อ

มะเร็งต่อมสร้างน้ำเลี้ยงอสุจิริยะแรกในลิงวอก: รายงานสัตว์ป่วยและการทบทวนวรรณกรรม

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มะเร็งต่อมสร้างน้ำเลี้ยงอสุจิริยะแรกถูกวินิจฉัยพบโดยบังเอิญ ระหว่างการตรวจทางจุลพยาธิ จากชิ้นส่วนเนื้อเยื่อของลิงวอกสายพันธุ์อินเดีย อายุ 9 ปี เพศผู้ ตลอดช่วงชีวิตของลิงวอกตัวดังกล่าว ได้ถูกใช้ในการทดลองโรคติดเชื้อหลายงานวิจัย และในท้ายสุดได้ถูกใช้ในการทดลองปลูกถ่ายเนื้อเยื่อไต ที่สถาบันวิจัยวิทยาศาสตร์การแพทย์ทหาร การวินิจฉัยนี้พบโดย นักพยาธิวิทยาทางสัตวแพทย์ผู้เชี่ยวชาญ (board certified: ACVP) เนื่องด้วยมีการปรากฏของเซลล์เนื้องอกจากการตรวจด้วยกล้องจุลทรรศน์ และทำการยืนยันผลการตรวจ โดยใช้วิธีทางอิมมูโนพยาธิวิทยา (immunohistochemistry) รายงานนี้ถือเป็นครั้งแรกที่มีการรายงานมะเร็งต่อมสร้างน้ำเลี้ยงอสุจิริยะแรกในลิง

คำสำคัญ: มะเร็งชนิดต่อม จุลพยาธิวิทยา ชนิดร้ายแรง ลิงวอก ต่อมสร้างน้ำเลี้ยงอสุจิ

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