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CASE REPORT

Tubulopapillary Adenocarcinoma of the Mammary Gland in an Amazon Jaguar (*Panthera onca)*

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ABSTRACT

A 17-years-old, female Amazon jaguar (*Panthera onca)* was presented for a subcutaneous mass of the mammary gland. Surgical excision and microscopic examination of the mass was performed. Histopathologically, the mass was uncapsulated and composed of tubulopapillary lobules of atypical round to polygonal epithelial cells. Tumor cells showed invasive growth into the connective tissue of the dermis and mitotic figures were frequently observed. Tumor cells also showed diffusely strong positive for cytokeratin (CK) AE1/AE3, proliferation cell nuclear antigen (PCNA) and Ki-67 antibodies. But, CK14, vimentin and P63 immunoreactivity was mainly expressed in the myoepithelial cell layer. Based on these pathological findings, present case was diagnosed as tubulopapillary adenocarcinoma of the mammary gland of Amazon Jaguar (*Panthera onca*).

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INTRODUCTION

The neoplasia of genus *Panthera* of the family Felidae has rarely been reported. Previous reports of tumor of jaguar included glucagonoma (Ramos-Vara *et al*., 2000), visceral mast cell tumor (de Castro *et al*., 2003), and multiple neoplasia (Frazier *et al*., 1994). It has been reported that mammary mucinous carcinoma in an African lion metastasized to various organs (Cagnini *et al*., 2012).

Immunohistochemistry is useful method for identification of neoplasms and their origins. Proliferating cell nuclear antigen (PCNA) is a nuclear protein which has maximal concentration in the G1 and S phases of the cell cycle. Also, Ki-67 is nuclear protein present in active parts of all cell cycle. PCNA and Ki-67 are mainly used to evaluating cell proliferation (Ozmen *et al*., 2008). The nature of tumor cell could be differentiated with AE1/AE3 (epithelial cell marker), CAM5.2 (epithelial cell marker), CK14 (myoepithelial cell marker), and vimentin (myoepithelial cells and mesenchymal cells marker) (Toniti *et al*., 2010). In this case report, we describe histologic and immunohistochemical features in a case of tubulopapillary adenocarcinoma of mammary gland of Amazon Jaguar (*Panthera onca)*.

Case history, examination and findings: A 17-years-old intact female Amazon jaguar *(Panthera onca)* that weighed about 80 kg, was referred to the Veterinary Medical Teaching Hospital of Kyungpook National University with a history of slightly anorexia and ataxia for the last few weeks. Physical examination revealed single subcutaneous mass (13 cm in diameters) with ulcer at the left fifth mammary gland (Fig. 1-A). Metastatis was not confirmed by radiography and sonography. The mass showed well demarcated, moveable, no adhered with deep tissue and large multiple ulceration with serosanguineous exudate were also seen. The jaguar had been treated with antibiotics for several weeks. Mastectomy was performed to remove the mass. The tumor mass was then submitted for histopathological examination. In cut section, the mass were well demarcated, multilobulated, grayish white with partial hemorrhage and necrosis (Fig. 1-B).

Excised tissues were fixed in 10% neutral-buffered formalin solution, embedded in paraffin according to a conventional method, sectioned about 3 μm thick were cut and mounted on glass slides. Sections were stained with hematoxylin and eosin (HE) and serial sections were

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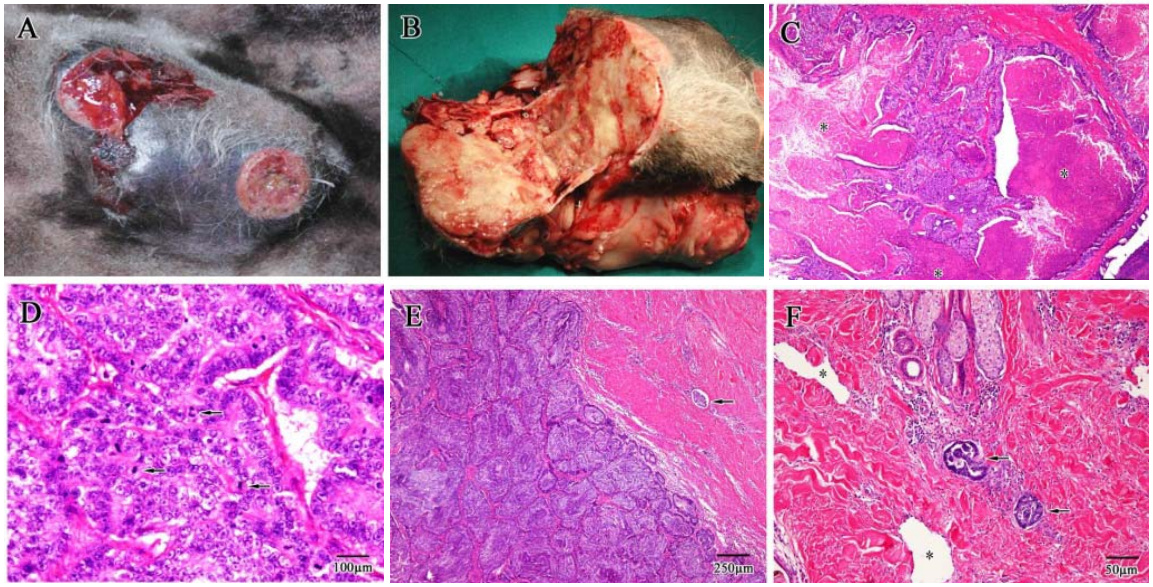

Fig. 1: Macroscopic and histopathological findings. As gross, single subcutaneous mass with hemorrhage was observed in the mammary gland (A). The cut surface of the subcutaneous mass was grayish white and hemorrhagic areas with necrosis were observed (B). The subcutaneous mass divided into lobules by thin fibrous stroma and the center of the tubules filled with the cell debris and eosinophilic secretes (*) (C). The nuclei of tumor cells were round to ovoid and mitotic figures (arrows) were frequently observed (D). Tumor cells showed infiltrative growth into the surrounding connective tissue and invasion within lymphatic vessels (arrow) were seen (E). Small nests of tumor cells infiltrated into the collagenous dermis (arrows). Dilated lymphatic vessels (*) were also seen (F).

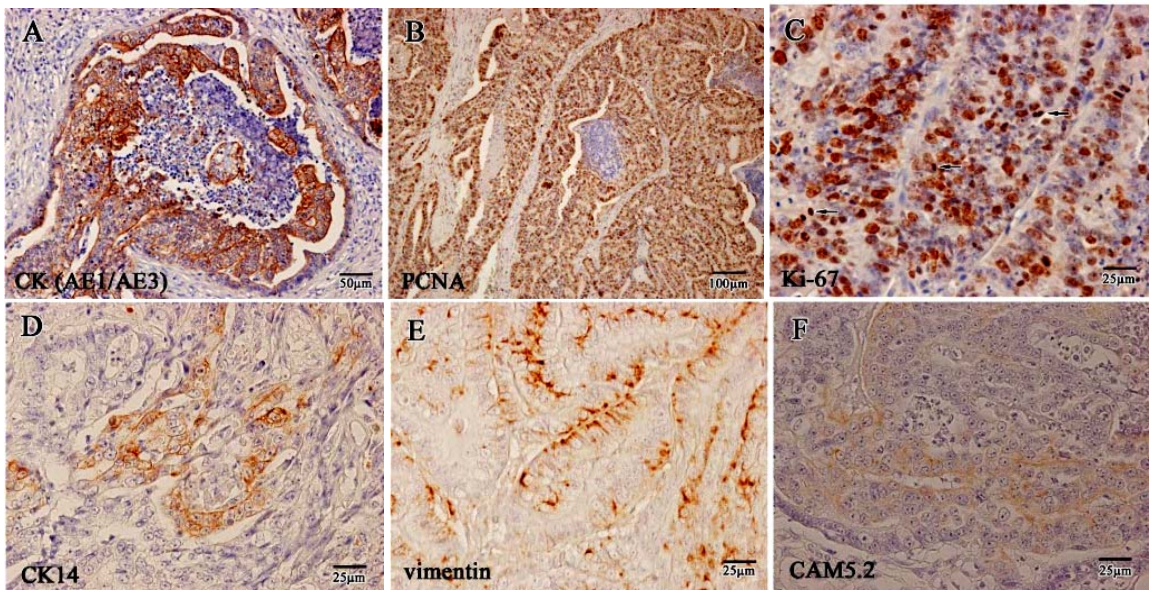

Fig. 2: Immunohistochemical findings. Most of tumor cells stain positively for CK AE1/AE3 (A). Most of tumor cells were stained positively for PCNA (B). Many of the nuclei and mitotic figures (arrows) of the tumor cells were positively stained for Ki-67 (C). Occasionally, tumor cells were positive for CK14 (D). Basal layer of the tubules were only stained for vimentin (E). Tumor cells reacted with antibody to CAM5.2 (F).

prepared for immunohistochemistry. The following primary antibodies were used: cytokeratin (CK) AE1/AE3 (Zymed, Carlsbad, CA, USA), CK14 (Thermo Fisher Scientific, Fremont, CA, USA), CAM5.2 (Becton Dickinson, CA, USA), α-smooth muscle actin (SMA) (DAKO, Glostrup, Denmark), vimentin (Nichirei, Tokyo, Japan), proliferaion cell nuclear antigen (PCNA) (DAKO, Carpinteria, CA, USA), P63 (Thermo Fisher Scientific, Fremont, CA, USA) and Ki-67 (DAKO, Carpinteria, CA, USA). Each antibody was visualized using 3-3'-diaminobenzidine (DAB, Dako, Japan). Slides were counterstained with hematoxylin.

Histopathologically, the subcutaneous mass located in the mammary gland was divided into lobules by thin fibrous stroma. Tumor cells formed acinus and tubular structures and partial papillary projections. The center of the tubules was filled with the cell debris and eosinophilic secretes (Fig. 1-C). Some acinus produced lactating materials, and sometimes formed large cysts. The tumor cells had round to ovoid and constricted hyperchromatic nuclei. Eosinophilic cytoplasm was relatively narrow and cuboidal shape. Mitotic figures were observed at the rate of over 5 per one field at ×400 magnification (Fig. 1-D). Tumor cells showed infiltrative growth into the

surrounding connective tissue (Fig. 1-E) and collagenous dermis (Fig. 1-F). Occasionally, tumor cells were found within adjacent lymphatic vessels. There were no neoplastic changes of myoepithelial cells and no differentiation to the chondroid or bone tissues.

Immunohistochemically, most of the tumor cells were stained positively for AE1/AE3 (Fig. 2-A), PCNA (Fig. 2-B), and 50-70% of the cells were positive for Ki-67 (Fig. 2-C) antibodies. Approximately 10% of tumor cells aligning innermost in the tubules expressed CK14 (Fig. 2-D). Myoepithelial cells located at the periphery of some neoplastic lobules and a part of cuboidal cells in the tubules were stained for SMA (data not shown), vimentin (Fig. 2-E) and P63 (data not shown) antibodies. Tumor cells and myoepithelial cells slightly react with CAM5.2 antibody (Fig. 2-F). Based on these histopathological and immunohistochemical observations, this tumor diagnosed as tubulopapillary adenocarcinoma of the mammary gland.

DISCUSSION

Lifelong sex hormonal exposure may influence tumorigenesis and tumor progression. Longevity also regarded as one risk factor of the mammary gland tumor. Geriatric jaguars (>16 years), especially in female, were highly prevalent in reproductive disease (Hope and Deem, 2006). In this case, the jaguar was sexual intact and 17 years old and she could be considered to geriatrics.

There were some reports that melengestrol acetate (MGA) treatment as contraception has close link with increase in the risk of mammary cancer. According to the other reports, regardless of MGA exposure, jaguars have higher prevalence of mammary gland cancer than other felids (Hope and Deem, 2006; McAloose *et al*., 2007). She was adapted in the owner's zoo 12 years ago and there have been no administration history of MGA. Another risk was proposed as carnivores are at the top of the food chain, they could have high chance of exposure to the diet contained environmental carcinogens or high level harmful hormones. In the literature, regardless of MGA administration, tubulopapillary pattern was most common and majority of mammary carcinomas were multiple histologic pattern (Munson and Moresco, 2007). In this case, tubulopapillary pattern which has varying sized tubes was prevalent and, although necrosis was observed in some areas, combinations with other pattern, such as solid or comedone form, were not shown.

Immunohistochemically, the expression of Ki-67 was strong (50~70%), especially in the tumor cells showing mitotic figure, and PCNA positivity was also observed in most cells. These findings support that the tumor is highly malignant and aggressive. Similarly, it was reported that most zoo felids had a high grade cancer with comparable aggressive metastasis regardless of treatment of MGA or not (McAloose *et al*., 2007).

Mammary gland epithelium is mainly consisted with two layer; basal/myoepithelial layer and inner luminal layer. To identify the nature of tumor cells, the expression pattern of AE1/AE3, vimentin, and CK14 needs to be examined. As a result, strong expression of AE1/AE3 was seen in epithelial cell. Tumor cells were diffusely positive for CAM5.2. Myoepithelial cells stained positively for SMA and vimentin were mainly located at the periphery of neoplastic lobules. Although infiltrative growth to surrounding tissue could be seen, most proliferative tumor cells were surrounded by a layer of myoepithelial cells that did not present neoplastic proliferations. CK14 was detected with slight and diffused positivity in some neoplastic cell. Attenuated vimentin and CK14 reaction could imply that the tumor was invasive (Sopel, 2010) and luminal to myoepithelial ratio was increased. According to these findings, most tumor cells thought to be originated in luminal cells, not in basal or myoepithelial cells.

During 6 months follow-up after surgical excision, no sign of tumor recurrence was observed and the jaguar remained clinically well. After 9 months from the operation, the jaguar was suddenly dead. Postmortem necropsy could not be performed and additive data or samples could not be collected. Therefore, we cannot identify the cause of mortality or the fact of recurrence or metastasis to the other organs.

Conclusion: Based on the histopathologic and immunohistochemical findings, it was concluded that the tumor of jaguar was simple adenocarcinoma which is classified as tubulopapillary, and it may be useful to understand the characteristics of mammary gland tumor in jaguar.

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