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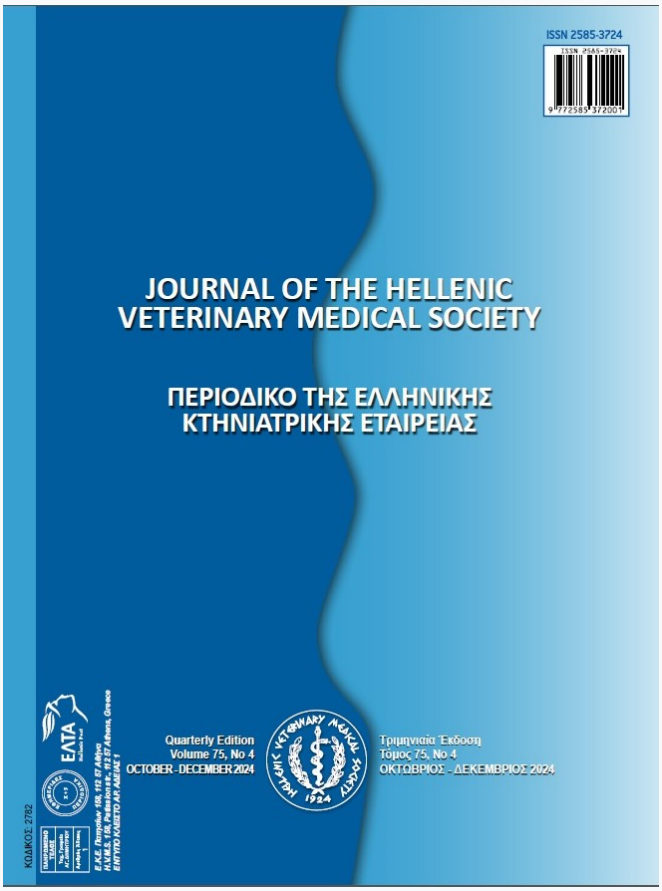

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Case report
Κλινικό περιστατικό

Amphophilic-vacuolar renal tubule adenoma in a 10-week-old female Sprague-Dawley rat

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ABSTRACT: Amphophilic-vacuolar (AV) tumors are variants of renal tubule (RT) tumors that show morphological characteristics that are distinguished from those of conventional renal tubule tumors. AV tumors are spontaneous and non-treatment-related because of their familial origin, whereas RT tumors are spontaneous or chemically induced. Limited data are available on the occurrence of AV tumors in young Sprague-Dawley (SD) rats. We reported AV RT adenoma in a 10-week-old female SD rat. The affected animal was a 10-week-old female SD rat during a 4-week repeated toxicity experiment. The kidneys of the rat were fixed in 10% neutral buffered formalin, processed routinely, stained with hematoxlin and eosin, and examined microscopically. A small solid mass was accidentally found in the cortex of the right kidney of the rat. The mass was well-demarcated and unencapsulated. It had a lobular pattern separated by a thin stand of fibrovascular stroma and was composed of large, round to polyhedral cells, with an amphophilic to lightly eosinophilic cytoplasm, which had large vacuoles, small lumens, and few lymphocytes. Large vesiculated nuclei contained prominent nucleoli. Part of the tumor was compressed from the capsule and surrounded by lymphocytic infiltrates. Additionally, a few mitotic figures and apoptotic bodies were observed. This rat was diagnosed with AV RT adenoma based on histological findings. In toxicity studies, it is crucial to differentiate AV tumors from RT tumors to determine whether they are spontaneous or treatment-related, especially in the highest test-substance dose group. This study provides an example of an AV tumor background in an SD rat.

Key words: Amphophilic-vacuolar renal tubule tumor; Neoplasm; Sprague-Dawley rat

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INTRODUCTION

Amphophilic-vacuolar (AV) tumors are variants of renal tubule (RT) tumors that have a distinct morphologic phenotype, which is differentiated from that of the conventional RT tumor in carcinogenicity studies in rats. AV tumors arise spontaneously, unrelated to treatment, owing to their hereditary basis, while RT tumors may arise spontaneously or due to chemical exposure (Hard et al., 1994; 2008). Spontaneous RT tumors with AV morphologic characteristics were first reported in Long Evans rats by Eker (Eker, 1954). Later, it was determined that this was due to a tuberous sclerosis gene mutation (Tsc2) (Kobayashi et al., 1995). A morphologically similar tumor case has been reported in Sprague-Dawley (SD) rats with a mutation in the Birt-Hogg-Dube tumor suppressor gene (Kouchi et al., 2006). Researchers have reported AV tumors in 90-day studies in rats (Hard et al., 1994; Hall et al., 2007; Lanzoni et al., 2007), subchronic toxicity studies in rats (2 weeks to 6 months) (Crabbs et al., 2013), and 2-year carcinogenicity studies (Hard et al., 2008). However, regarding the occurrence of AV tumors in young SD rats (less than 10-week-old) are less available, we reported AV RT adenoma in a 10-week-old female SD rat.

CASE HISTORY

A 10-week-old female SD purchased from Orient Bio Inc. (Seongnam-si, Gyeonggi-do, Republic of Korea) was assigned to the high-dose group during a 4-week repeated toxicity study. The rat was housed in a stainless-steel cage at 19-25°C, a relative humidity of 30%-70%, and a 12:12 h light: dark cycle, and supplied with a commercial rodent diet and purified autoclaved water *ad libitum*. The study protocols were conducted in accordance with Organization for Economic Co-operation and Development (OECD) guidelines for the testing of chemicals, "Test No. 407: Repeated Dose 28-Day Oral Toxicity Study in Rodents" and approved in accordance with Institutional Animal Care and Use Committee Guidelines (Accepted No.: ABIACUCRA22153).

At necropsy, the kidneys showed no gross lesions and were surgically collected, fixed immediately in 10% neutral buffered formalin, processed routinely, embedded in paraffin, sectioned at 3-4 μm, stained with hematoxylin and eosin (HE), and examined microscopically.

A small solid mass was observed in the cortex of the right kidney. The mass was well-demarcated and unencapsulated. It had a lobular pattern separated by a thin strand of fibrovascular stroma and was composed of large, round to polyhedral cells, with an amphophilic to lightly eosinophilic cytoplasm, which had large vacuoles and few lymphocytes. Large vesiculated nuclei often had prominent nucleoli. Part of the tumor was compressed from the capsule and surrounded by lymphocytic infiltrates. Additionally, a few mitotic figures and apoptotic bodies were observed (Figure 1). However, the left kidney appeared normal histologically appearance.

DISCUSSION

RT tumors have variable patterns, including solid, tubular, cystic, lobular, papillary, cystic papillary, and mixed solid. The cells are composed of a basophilic cytoplasm with infrequent vacuoles and occasional minilumens. The nucleoli are often prominent, not inclusion-like, and the mitotic rate is variable but high in the carcinoma. RT tumors are more commonly observed in males, and mainly older rats. However, its association with severe chronic progressive nephropathy (CPN) has not been reported. Metastases have been reported in carcinoma of 2 cm and larger (Crabbs et al., 2013). In contrast, AV tumors are characterized by a uniform lobular pattern in which the lobules are distinguished by a thin fibrovascular stroma. The lobules consist of large, round to polyhedral cells with amphophilic to eosinophilic cytoplasm, and the cells frequently contain large vacuoles and/or mini lumens. Nucleoli are often prominent, and sometimes inclusion-like and lymphocytic infiltrates are common. The mitotic rate is low. AV tumors are commonly found in female, young and old rats. However, it has not been reported to be associated with CPN or metastasis (Hard et al., 2008). In the present case, the tumor was expansile, non-encapsulated, and could be classified into an adenoma. Thus, this lesion was diagnosed as AV RT adenoma based on histological findings.

The occurrence of AV tumors in subchronic toxicity studies may not be related to the effects of the test substance in experimental groups because AV tumors have been reported to be spontaneous and non-treatment-related with familial origin, whereas RT tumors are spontaneous or chemically induced (Hard et al., 2008). Therefore, AV tumors should be differentiated from RT tumors. The incidence of AV tumors was 0.1% and that of RT tumors was 1.1% in the National Toxicology program 2-year carcinogenicity study (Hard et al., 2008). In contrast, the incidence of AV

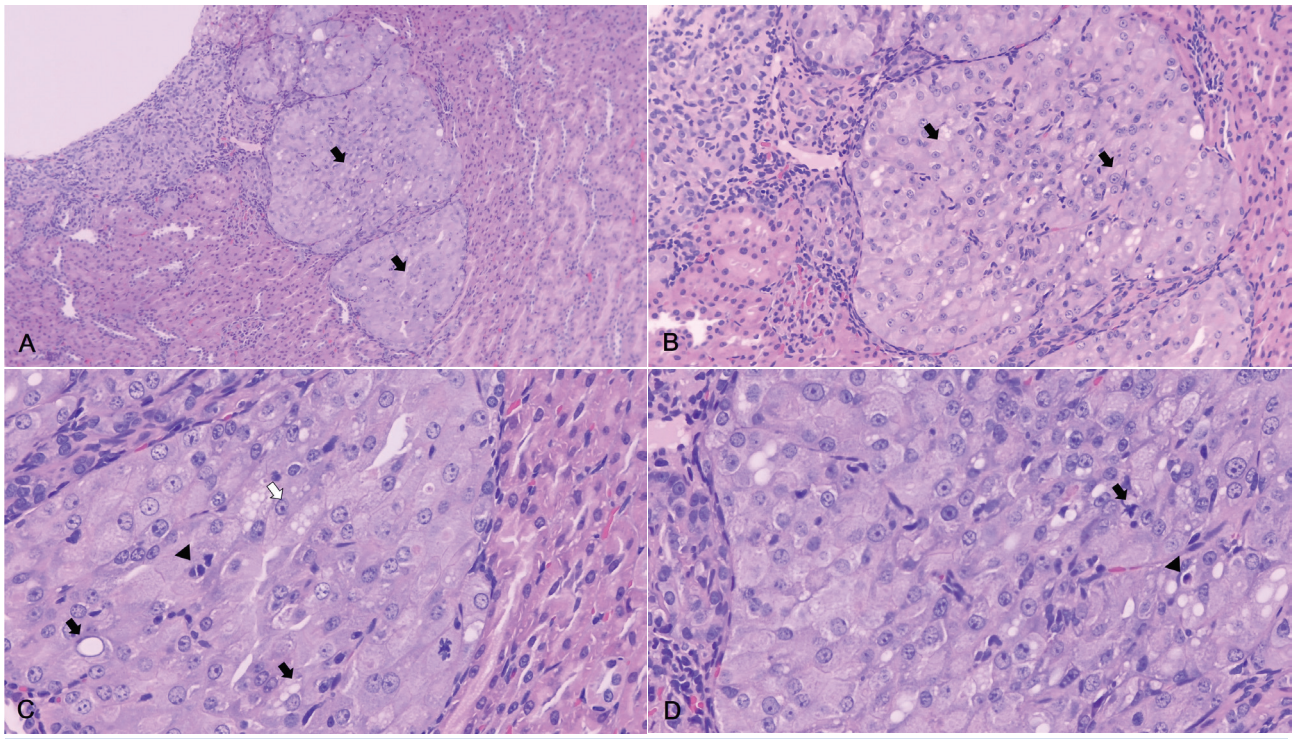

Figure 1. Histological findings of the tumor in the kidney. A) The mass is well- demarcated, and unencapsulated. It has a lobular pattern separated by a thin strand of fibrovascular stroma (arrow). ×100. B) The mass is composed of large, round to polyhedral cells, with amphophilic to lightly eosinophilic cytoplasm (arrow). ×200. C) The cytoplasm has large and small vacuoles (arrow) and few lymphocytes (arrow head). Large vesiculated nuclei often have prominent nucleoli (white arrow). ×400. D) Mitotic figure (arrow) and apoptotic body (arrow head) in the cytoplasm. ×400, HE.

tumors was 64.9% and that of RT tumors was 35.9% among renal tumors in toxicity studies of five surveyed laboratories (Crabbs et al., 2013). This study indicated that awareness of AV tumor has increased since Hard et al (2008). AV tumors have also been reported in male SD rats fed a diet containing genetically modified maize in a pathology working group peer-reviewed 13-week toxicity study. They concluded the tumors were spontaneous and unrelated to the test substance because AV tumors feature a familial origin (Hardisty et al., 2013). Renal tumors with the same characteristics as AV tumors have not been reported in other species, including humans. However, renal tumors with morphological similarity to AV tumors were observed in 26-week Tg.RasH2 mouse carcinogenicity studies, although they were spontaneous but, not familial-origin because they were not tracked to parent mice (Paranjpe et al., 2016), whereas AV tumors in SD and Fischer 344 rats were considered to be familial-origin (Crabbs *et al.*, 2013; Hard *et al.*, 2008). In 2-weeks to 6-month toxicity studies survey, the proportion of AV tumors increased among RT tumors in younger rats (Crabbs et al., 2013). However, further information is needed because the number of young rats with AV tumors is limited in this literature.

In conclusion, although AV tumors have been reported in the literature, they are rarely documented in young rats (Crabbs et al., 2013). AV tumors should be differentiated from RT tumors in toxicity studies because determining whether they were spontaneous or treatment-related is important, particularly in the highest test-substance dose group. This case report provides an example of an AV tumor background in an SD rat.

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CONFLICT OF INTEREST

None declared

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