A Case Report of a Renal Mixed Epithelial and Stromal Tumor in a Heterozygous S1P2 Receptor Deficient Mouse

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ABSTRACT: We report a case of mixed epithelial and stromal tumor of the kidney (MESTK) in a 32-week-old heterozygous sphingosine 1-phosphate-2 (S1P2) receptor deficient female mouse. A white solid mass replacing the left kidney was observed at the left retroperitoneal wall. Histologically, the tumor mass consisted of dimorphic cellular components of epithelial and stromal cells. Epithelial cells formed various sized irregular-shaped tubular structures resembling renal tubules surrounded by stromal cells. Immunohistochemically, epithelial cells were positive for cytokeratin, while stromal cells showed positive immunoreactivity with α-smooth muscle actin as well as vimentin. Based on the morphological and immunohistochemical findings, this tumor was diagnosed as a MESTK.

KEY WORDS: N-ethyl-N-nitrosourea, renal mixed epithelial and stromal tumor, S1P2 deficient mouse.

This report describes a case of mixed epithelial and stromal tumor of the kidney (MESTK) in a female heterozygous sphingosine 1-phosphate-2 (S1P2) deficient C57BL/6N mouse of 32 weeks old. S1P2 is a member of the G protein-coupled receptor family (formerly called the EDG family) that binds and mediates a variety of actions of sphingosine-1-phosphate, a plasma-derived pleiotropic sphingolipid mediator. A heterozygous S1P2-deficient female mouse which received a single subcutaneous injection of 120 mg/kg body weight of N-ethyl-N-nitrosourea (ENU) at 6 weeks of age was subjected to complete necropsy on 32 weeks of age. Until necropsy, this mouse did not show any abnormal clinical signs. At necropsy, a white solid mass (15 mm × 10 mm × 10 mm) replacing the left kidney without involving the surrounding tissues was observed at the left retroperitoneal wall. While 3 groups of mice including wild type mice (n=14), heterozygous S1P2 deficient mice (n=9), and homozygous S1P2 deficient mice (n=8), all given ENU, were allocated, such a renal tumor was not observed in the other ENU-treated mice. On cut section, a mass was white, firm and mottled with hemorrhagic foci. No other particular pathologic abnormalities were observed in this mouse. The mass was fixed in 10% neutral buffered formalin and processed for routine histopathology with hematoxylin and eosin. Periodic acid-Schiff (PAS) staining was also applied on this tumor. As immunohistochemical analysis, avidin-biotin-peroxidase complex (ABC) technique was applied using antibodies against α-smooth muscle actin (monoclonal mouse antibody, clone 1A4; DAKO, Glostrup, Denmark), cytokeratin (monoclonal mouse antibody, clone MFN116; DAKO), desmin (monoclonal mouse antibody, clone D33; DAKO), estrogen receptor (monoclonal mouse antibody, clone 6F11; Novocastra Laboratories, Newcastle upon Tyne, UK), vimentin (polyclonal goat antibody, product no.C-20, Santa Cruz Biotechnology, Santa Cruz, CA) and WT-1 (polyclonal rabbit antibody, product no.C-19, Santa Cruz Biotechnology). These slides were lightly counterstained with hematoxylin. Appropriate positive and negative control tissues were included in all of the immunostainings.

The histological examinations revealed that the mass consisted of dimorphic cellular components of epithelial and stromal cells (Fig. 1). Epithelial cells formed various sized irregular-shaped tubular or cystic structure resembling renal tubules lined by cuboidal to columnar cells with clear to eosinophilic cytoplasm. Scattered formation of large cysts was lined by hobnail-shaped cells (Fig. 2). Hemorrhage was observed in some of these cysts. Epithelial tubular structures were surrounded by stromal cells that often form bundled and woven cellular arrangements sometimes along with prominent vessels, and myxoid change was seen in some of the area where stromal cell proliferation was prominent. These stromal cells were mostly spindle-shaped cells, which were morphologically similar to smooth muscle cells (Fig. 3). These epithelial and stromal cell components showed mild cellular atypia with occasional mitotic figures. Some massive necroses were detected in the tumor, but neither invasions into the capsule nor metastases were observed. This tumor had no blastic component that is a hallmark of the nephroblastoma. There were no normal renal tissues within this tumor mass. With PAS staining, neither basal membranes nor brush borders suggesting proximal tubules were observed in these tubular structures. Immunohistochemical analysis revealed that epithelial cells were positive for cytokeratin (Fig. 4), while stromal cells were positively stained with both vimentin (Fig. 5) and α-
Fig. 1. Kidney tumor; mouse. The tumor consists of epithelial and stromal cell components. Epithelial cells form various sized irregular-shaped tubular structures resembling renal tubules or cysts. HE stain. × 100.

Fig. 2. Kidney tumor; mouse. Note large cyst lined by hobnail-shaped cells. HE stain. × 400.

Fig. 3. Kidney tumor; mouse. Spindle-shaped stromal cells are morphologically similar to smooth muscle cells, showing arrangement in bundled and woven patterns. HE stain. × 200.

Fig. 4. Kidney tumor; mouse. The cytoplasm of epithelial cells forming tubules and cysts is positive for cytokeratin. Immunohistochemical stain of cytokeratin antigen. Avidin-biotin-peroxidase complex (ABC) technique with hematoxylin counter-stain. × 200.

Fig. 5. Kidney tumor; mouse. Stromal cells are strongly positive for vimentin. Immunohistochemical stain of vimentin antigen. ABC technique with hematoxylin counter-stain. × 200.

Fig. 6. Kidney tumor; mouse. Stromal cells are strongly positive for α-smooth muscle actin. Immunohistochemical stain of α-smooth muscle actin antigen. ABC technique with hematoxylin counter-stain. × 200.
smooth muscle actin (Fig. 6). Neither epithelial nor stromal components were positive for desmin, estrogen receptor or WT-1.

Renal tumors composed of epithelial and mesenchymal components without blastemal cells do not fit any of the domestic animal renal tumors, other than hamartomas, as described in the WHO classification [7]. Hamartomas are benign tumor-like nodules composed of disorderly and excessive growth of mature cells and tissues normally present in the affected part. A case report of hamartoma described in 8-month-old Holstein heifer is quoted in this WHO classification. This was a circumscribed mass in 0.5 cm in diameter and composed of poorly organized tubules, glomeruloid structures, and disorganized spindle cells in collagenous stroma with vessels lined by hypertrophic endothelial cells [5]. Although these histological appearances of hamartoma partly resemble our case, the lack of specific structures such as glomeruli and brush borders of proximal tubules, and mild atypia and occasional mitotic figures in the present case strongly suggest that this lesion must be a benign renal tumor. Furthermore, hamartomatous appearance with tumor aspects is considered to be a characteristic feature of MESTK, because this tumor had also been known as a cystic hamartoma of the renal pelvis according to the previous WHO classification of human [11].

MESTK in human is a rare renal tumor which was first described by Michal and Syrueck in 1998 [9]. In human pathology, MESTK was first described in the WHO classification in 2004 [6]. MESTK occurs over a wide age range but especially in perimenopausal age in females, and is 4 to 5 times more common in females than males [13]. Pathologically, MESTK is a well circumscribed biphasic tumor composed of spindle cell stroma and variously sized gland-like structures ranging from small tubules to cystic structures lined by hobnail-shaped epithelia that are typical of renal collecting ducts [8, 13]. Immunohistochemically, spindle cells stained consistently with vimentin and α-smooth muscle actin. In contrast, desmin was more patchy. Epithelial cells reacted with antibodies to cytokeratin [10, 13]. As some spindle cells of MESTKs were immunoreacted with estrogen and/or progesterone receptors, hormones are thought to play a role in the pathogenesis of MESTKs [1]. Although we could not obtain a positive result for estrogen receptor antigen in our case, it has been hypothesized that this tumor is possibly derived from the Mullerian/paramesonephric rest [1]. The paramesonephric remnants, originating from the Mullerian duct which has close relations to the kidney and upper urothelial tract may be the origin, and perimenopausal events or hormonal therapy against menopause may trigger tumorigenic transformation of this bud [1]. In animals, only one case of MESTK has been reported in a female Ringtail Lemur [12]. Neither estrogen nor progesterone receptors were immunohistochemically identified in this case. Based on the morphologic and immunohistochemical findings of MESTK in the WHO classification in human [6] and the case report on a Ringtail Lemur, the present case can be diagnosed as a MESTK in mice.

There was a conflict in the tumor growth pattern between MESTK in humans that was observed as a solitary nodule/mass in the kidney and our case that completely replaced the left kidney. It is not clear whether the ENU administration influenced the oncogenesis of this renal tumor in mice. Although renal tumors such as nephroblastomas and mesenchymal tumors induced by administration of ENU have been reported in rats [3], there have been no reports regarding ENU-induced renal tumors in mice. In addition, similar tumors were not observed in any other mice given ENU in the present study. Antiproliferative activities of S1P, the ligand for EDG family receptors, were reported in mouse myoblasts or human myofibroblasts through S1P2 [2, 4]. Nevertheless, similar tumors were not seen even in homozygous S1P2 deficient mice. Thus, ENU-treatment and gene-targeting of S1P2 may not be a primary cause for induction of this tumor. However, it is likely that these factors play a role as tumor promoters that can enhance the growth of tumor buds and enlarges an intrinsically well-circumscribed tumor of this type.

REFERENCES