Mixed Epithelial and Stromal Tumors of the Kidney

An Overview

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Mixed epithelial and stromal tumor of the kidney is a recently recognized distinct neoplasm that should be distinguished from other renal neoplasms. These tumors are relatively rare with a female preponderance. Imaging studies are not diagnostic but reveal a solid or solid and cystic mass in most cases. Histopathologically, these tumors reveal biphasic growth pattern comprising mesenchymal and epithelial elements with characteristic estrogen and progesterone receptor immunoreactive mesenchyme reminiscent of ovarian stroma. Malignant transformation, recurrence, and metastasis are rare; however, recently a few cases of malignant mixed epithelial and stromal tumors have been reported in the literature. Recently a case with translocation t(1;19) has been described. This article provides a brief overview of the current knowledge of mixed epithelial and stromal tumor of the kidney.

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Adult renal neoplasm with a variable admixture of epithelial and mesenchymal components is a distinctive benign neoplasm that has recently been recognized and termed as benign mixed epithelial and stromal tumor (MEST) by Michal and Syrueck1 and Adsay et al.2 These tumors are relatively rare and only isolated case reports and small series are available in the literature.3–11 These tumors have been published under the following names in the literature: leiomyomatous renal hamartomas, congenital mesoblastic nephroma in an adult, cystic hamartoma of renal pelvis, solitary multilocular cysts of the kidney, multilocular renal cyst with müllerian-like stroma, and adult metanephric stromal tumor.6,11 More recently, the term MEST has been proposed for these neoplasms.11 Patients with MEST range in age from 19 to 78 years with a female preponderance (male to female ratio, 1:10). Patients usually present with a palpable abdominal or flank mass, flank pain, and/or hematuria. In a recent study, most were incidental findings.1–11 Imaging studies are not diagnostic but reveal a centrally located solid or solid and cystic mass in most cases.

CLINICAL FEATURES

Patients range in age from 19 to 78 years with a female preponderance (male to female ratio, 1:10). Patients usually present with a palpable abdominal or flank mass, flank pain, and/or hematuria. In a recent study, most were incidental findings.1–11 Imaging studies are not diagnostic but reveal a centrally located solid or solid and cystic mass in most cases.

PATHOLOGIC FEATURES

Macroscopic Features

Gross pathologic examination of MEST reveals variably solid and cystic, tan to yellow, well-circumscribed, but rarely encapsulated lesions ranging from 2 to 24 cm. In some cases, a cystic component predominates and is associated with solid mural nodules,6,11 whereas in others the macroscopic appearance may mimic multilocular cystic renal cell carcinoma.11 Involvement of renal hilum and compression of the pelvicaliceal system is common; however, gross infiltration into adjacent renal parenchyma is not seen in benign MESTs. Mixed epithelial and stromal tumor rarely involves sinus fat. Areas of heterogeneity including necrosis and calcification may be observed occasionally.4

Microscopic Features

The tumor is classically biphasic comprising mesenchymal and epithelial elements. The mesenchymal component is characterized by fascicles of spindle cells showing variable degrees of smooth muscle, fibroblastic, or myofibroblastic differentiation associated with interspersed bundles of collagen. It most often resembles the classical form of cystic nephroma (CN) or fibromatosis (Figures 1 and 2). The mesenchymal component resembling that of ovarian stroma (Figure 2) and focal changes of the stromal cells reminiscent of ovarian stromal cell luteinization have been described.11,12 The epithelial component is an integral part of the neoplasm that may be observed interspersed throughout the mesenchymal components and not merely restricted to the periphery of the tumor nodules. The epithelial components vary from round and regular tubules to more complex tubulopapillary structures with or without cystic dilatation (Figure 3). These are lined by cuboidal to flattened epithelium that may show clear cell change (Figure 4) and have a characteristic hobnail appearance. Mitotic figures, hemorrhage, and necrosis have not been described for the benign form of MEST. Malignant transformation, recurrence, and metastasis are rare in MEST;
Figure 1. The tumor showing characteristic biphasic pattern: mesenchymal and epithelial elements (hematoxylin-eosin, original magnification ×10).

Figure 2. The mesenchymal component resembling that of densely cellular ovarian stroma (hematoxylin-eosin, original magnification ×10).

Figure 3. The epithelial components in the form of round to angular to more complex tubular structures with cystic dilatation (hematoxylin-eosin, original magnification ×20).

Figure 4. Variously sized cysts lined by cuboidal to flattened epithelium with clear cell change (hematoxylin-eosin, original magnification ×10).

Figure 5. The mesenchymal cells showing immunoreactivity for smooth muscle actin (original magnification ×20).

Figure 6. The mesenchymal cells showing immunoreactivity for progesterone receptor (original magnification ×20).

However, recently a few cases of malignant MEST have been reported in the literature. The features of malignancy can be observed in either epithelial or mesenchymal components. These include increased cellularity, cytologic atypia, round to ovoid vacuolated nuclei with prominent nucleoli, and high mitotic rate (15 to 25 mitoses per 10 high-power fields). Rhabdoid, rhabdomyosarcomatous, and chondrosarcomatous components may be evident as well.13–15

**Immunohistochemistry**

The immunohistochemical profile of the mesenchymal component reflects smooth muscle differentiation (immunoreactivity for desmin and smooth muscle actin) (Figure 5). HMB-45 and CD34 stains are negative. The epithelial components are positive for both low- and high-molecular-weight cytokeratin and Ulex europaeus.4,9 Positive reactions with antibodies to estrogen and progesterone receptors have recently been described in the mesenchymal element in most cases11 (Figure 6). Although focal progesterone receptor expression has been described in malignant MEST, all cases of malignant MEST are negative for estrogen receptor expression. Estrogen and progesterone receptor expression are not by themselves diagnostic of MEST, and characteristic morphologic features should take precedence. Additionally, Turbiner et al12 demonstrated CD10, calretinin, and inhibin positivity in 77%, 69%, and 42% of MESTs, respectively, in their series of 14 cases.

**Ultrastructural Features**

Ultrastructural analysis reveals features of proximal tubular epithelium in some of the tubules, whereas other tubules have features of thin segment of loop of Henle leading one to assume that the tubules are entrapped and nonneoplastic. The mesenchyme shows variable degrees of smooth muscle, fibroblastic, or myofibroblastic differentiation associated with collagen.16

**Cytogenetics and Molecular Profile**

A recent case report showed an MEST that has translocation t(1;19).17 The histogenesis of this tumor is unknown, and it has been proposed that both components of the tumor, stromal and epithelial, are neoplastic. It has also been suggested that MEST might be the renal counterpart of similar mixed epithelial and stromal neoplasms that occur in the pancreaticobiliary apparatus because the latter are also characterized by cystic structures lined by epithelium, admixed with ovarian-like stroma.18

**PATHOGENESIS**

The female preponderance of MEST and history of long-term estrogen replacement in female patients or long-term sex-steroid exposure in male patients, combined with the frequent expression of estrogen and progesterone receptors in the mesenchymal component, suggest that the steroid hormones might play a role in the evolution of these tumors.11,18

**DIFFERENTIAL DIAGNOSIS**

The major differential diagnosis includes CN. There are striking similarities between CN and MEST in their clinical behavior, morphologic attributes of both the epithelial and stromal components, and immunohistochemical profiles although with variation in individual categories with higher prevalence of stromal to epithelial ratio, prominent ovarian stroma, smaller cysts with phyllodes glands pattern, and stromal luteinization being more prominent in MEST, and large cysts, thin septa, and low stromal to epithelial ratio in CN.12,19,20 The presence of ovarian-type stroma and müllerian related immunohistochemical markers raises the possibility that these 2 entities may originate from müllerian remnants misplaced during embryogenesis. A recent study by Antic et al20 showed that MEST had considerable morphologic overlap with CN and suggested that they may represent opposite ends of the spectrum of the same process. Furthermore, another multi-institutional study by Turbiner et al12 proposed a unifying term of “renal epithelial and stromal tumor” to encompass the spectrum of findings observed in MEST and CN at least until new molecular studies can prove or disprove this challenging hypothesis. Stromal predominant entities such as congenital mesoblastic nephroma and primary renal synovial sarcoma can be considered as differential diagnoses of MEST. Congenital mesoblastic nephroma is generally a solid mass composed of uniform spindle stromal cell components with rare entrapped renal tubules and is infiltrative at its interface with renal parenchyma; however, MEST is usually well circumscribed and extremely variable in appearance with fibroblastic areas, bands of smooth muscle, and the ovarian-like stroma. Recent studies have shown clearly that MEST lacks the genetic alteration of cellular congenital mesoblastic nephroma.11 Additionally, the morphology of malignant MEST warrants a strong consideration of multicytic renal cell carcinoma, primary renal synovial sarcoma, pure renal rhabdoid tumor, and primary renal sarcoma in the differential diagnosis. Lack of aggregates of clear cells in MEST helps differentiate it from multicytic renal cell carcinoma. Several features of malignant MEST are observed in primary renal synovial sarcoma, especially gross or microscopic cysts and tubules lined by hobnail epithelium, immunoreactivity for cytokeratin in the epithelial component, and variably dense spindle-cell stroma with occasional short fascicles and a moderate degree of mitotic activity.21–23 However, it should be noted that the typical tubules and cysts of MEST are entrapped renal tubules, and the latter are also characterized by cystic structures lined by epithelium, admixed with ovarian-like stroma.
ever, the prominent subepithelial condensation of the stroma (ovarian-like stroma) is a distinctive feature of MEST and is not observed in renal syovial sarcoma, and pri-
men re·nal syovial sarcoma in addition shows STY-SSX2 transcript.24,26,27 Furthermore, strong immunohistochemical positivity for expression of estrogen receptor is a distinctive feature of MEST, which is not observed in syovial sarcoma. The presence of rhabdoid features in malignant MEST poses difficulty in differentiating MEST from pure renal rhabdoid tumor. Morphologically, subepithelial condensation of ovarian-like stoma and tubular and cystic structures lined by hobnail epithelium are not characteristic of rhabdoid tumor.28 Adult rhabdoid tumor would not be expected to show strong estrogen receptor positivity by immunohistochemistry as demonstrated in MEST. Pri-
mary renal sarcoma, not otherwise specified, also needs to be considered as one of the differential diagnoses. Sar-
comas involving the kidney tend to entraps existing renal tubules sometimes causing them to dilate and form cystic structures. Although in malignant MEST typical areas of benign MEST may be difficult to find, the estrogen receptor–positive hypercellular stroma resembling ovarian stroma cuffing epithelial lined cysts aids in differentiating these 2 lesions.

TREATMENT AND PROGNOSIS

All reported cases of adult MESTs have behaved in a benign fashion following surgical excision, although one recurred locally 21 years after resection.2 The recurrent tumor invaded the liver and was composed exclusively of spindle cells.

CONCLUSION

In conclusion, MEST is a relatively rare and distinct neoplasms of the kidney that should be distinguished from other renal neoplasms. Although the overall prognosis is favorable, recurrence and malignant transformation of MEST can occur, and it is difficult to distinguish benign or malignant nature on imaging studies. Therefore, intraoperative frozen section is helpful when a partial nephrectomy is performed to exclude a positive margin, rather than to establish the nature of the tumor.

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