Mixed Epithelial and Stromal Tumor of the Kidney or Adult Mesoblastic Nephroma
An Update

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Purpose: Our aim was to review the spectrum of usual and unusual clinical and morphologic findings observed in mixed epithelial and stromal tumor of the kidney (MEST).
Materials and Methods: On the basis of MEDLINE database searches, we assessed all aspects of MEST or adult mesoblastic nephroma since the first report in 1997 till the end of 2009.
Results: Mixed epithelial and stromal tumor is a relatively rare and distinct neoplasm 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
Conclusion: It is difficult to distinguish benign or malignant nature on imaging studies.

Keywords: mesoblastic nephroma, renal cell carcinoma, diagnosis, pathology

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INTRODUCTION

Background

Classification of kidney tumors in adults expands rapidly with new categories recently being incorporated. A number of recently described and unusual entities such as familial renal cell carcinoma (RCC), translocation RCC, RCC after neuroblastoma, tubular mucinous and spindle cell carcinoma, and mixed epithelial and stromal tumors (MESTs) have been presented.[1] The term of "renal epithelial and stromal tumor" has been proposed to encompass cystic nephroma and mixed epithelial and stromal tumor of the kidney.[2]

Mixed epithelial and stromal tumor is a rare complex renal neoplasm composed of a mixture of cystic and solid components. It was originally described in 1993 by Pawade and colleagues as cystic hamartoma of the renal pelvis.[3] The term of "mixed epithelial and stromal tumor of the kidney" was proposed by Michal and Syrucek.[4] Other names such as adult mesoblastic nephroma (MN), leiomyomatous renal hamartoma, solid and cystic biphasic tumor, and cystic hamartoma of the renal pelvis have also been used.

Mesoblastic nephroma is an uncommon, distinctive renal tumor reported in infants. It is a special type of nephroblastoma that rarely occurs in adults. Mesoblastic nephroma was first described by Block and colleagues in adults in 1973,[5] but it is the most frequent renal tumor during the first year of life and the most frequent benign renal tumor in the

childhood. In children, MN is non-metastatic, well differentiated, amenable to surgical removal, and carries a good prognosis, but its origin is under debate.

Wigger regarded MN as a hamartoma,[6] while Bolande believed it originated from the renal blastema.[7] More recently, it was regarded as a tumor of the collecting ducts, but this has been shown to be untrue in a study by Daniel and associates.[8] Mesoblastic nephroma consists of classic and cellular (atypical) variants. There is no unanimous opinion on the biological behavior of MN because the tumor behaves differently. Until 1999, only 22 cases of adult MN of the kidney were reported.[9] Therefore, MN is poorly characterized in adults.

Objectives

The primary aim of this review was to assess morphologic features, including macroscopy, microscopy, immunoprophile, epidemiology, and clinical findings of MEST.

MATERIALS AND METHODS

Search Strategy

On the basis of MEDLINE database searches, we assessed all aspects of mixed epithelial and stromal tumor of the kidney or adult mesoblastic nephroma since the first report in 1997 till the end of 2009. Totally, the reports of 90 cases of MEST were found.

RESULTS

Morphologic Features

Macroscopy

Mixed epithelial and stromal tumors often arise centrally in the kidney and grow as expansile masses, frequently herniating into the renal pelvic cavity. The tumors are typically composed of multiple cysts and solid components and are 2 to 24 cm in size.[10,11] The largest tumor was reported by Moslemi; 25 cm in size and 5400 grams in weight with malignant behavior and fatal recurrence.[12] It was well circumscribed and partially encapsulated, and displayed a solid/cystic cut surface, with a predominantly solid component in most of them. One tumor was almost purely cystic. Most tumors extended to the renal sinus, and some appeared entirely intrapelvic on imaging studies; however, gross and microscopic evaluation did not show destructive invasion of the pelvic wall.[13]

Microscopy

Mixed epithelial and stromal tumors are complex tumors composed of large cysts, microcysts, and tubules. The largest cysts are lined by columnar and cuboidal epitheliums that sometimes form small papillary tufts. Urothelium, which may be hyperplastic, may also line some portions of the cysts. Mixed epithelial and stromal tumor's cytoplasm ranges from clear to pale, eosinophilic, or vacuolated.[14]

The architecture of the microcysts varies from simple microcysts to densely packed clusters of microcysts, or complex branching channels that may be dilated. The stroma consists of a variably cellular population of spindle cells with plump nuclei and abundant cytoplasm. Densely collagenous stroma is common and fat is occasionally present.[15-17] Extension of the tumor beyond the renal capsule has not been described.

Each tumor is composed of both epithelial and stromal components. The epithelial component, which displays no difference between the classic and cellular variants, is composed of isolated or clustered tubules and cysts, lined by a benign epithelium with a wide range of cytologic differentiation. The stromal cells are composed of fibroblasts, myofibroblasts, and smooth muscle cells in various combinations. Stromal cellularity is low for the classic variant, but high for the cellular variant. Hemorrhage, necrosis, and high mitotic index are noted in the stroma of the cellular, but not in the classic variant.[13]

Microscopic characteristics of MESTs are eosinophilic spindle cells with ovoid nuclei, which proliferate tightly and arrange in a bundle or wholly. Among tumor cells, tubule-forming columnar epithelial cells are scattered. Cartilaginous tissue and extramedullary hematopoiesis are sometimes recognized. Usually, the capsule of the tumor does not exist and tumor

cells proliferate to infiltrate the normal renal tissue.[13] The proposed histogenesis of this tumor is controversial.

Bolande suggested that maturation and differentiation of Wilms tumor and collagenization of the matrix leads to MEST.[7] Wigger proposed, from the observation with electron microscopy, that epithelial tissues are involved with tumor cells and the origin of epithelial elements and tumor cells are completely different.[6] Electron microscopic study shows tubules with various sizes surrounded by bands of smooth muscle cells. The cytoplasm of the epithelial cells contains numerous intermediate filaments. The genetic make-up of MEST differs from infantile MN by lacking ETV6-NTRK3 gene fusion or polypoid chromosomes 8, 11, and 17.[8,11,18]

Immunoprophile

Mixed epithelial and stromal tumors show immunoreactivity of the epithelial components with antibodies to cytokeratin, especially cytokeratin 7. The stromal component expresses vimentin, smooth muscle actin, caldesmon, and desmin. In general, CD10, calretinin, inhibin, and estrogen receptor (ER) and progesterone receptor (PR) expressions are seen in MESTs. The expression of PR is more extensive and is present in more cells in comparison with ER.[19] The uninvolved kidney does not express sex steroid receptors. Immunohistochemically, MN is consistently positive for myofibroblastic markers (vimentin, smooth muscle actin, and desmin) and negative for epithelial markers.[19] Immunohistochemical studies usually show strong positivity for cytokeratin in epithelial elements as well as desmin and smooth muscle actin in stromal elements. Both epithelial and stromal components are uniquely positive for vimentin, ER, and PR.

Malignant Transformation

Mixed epithelial and stromal tumors behave as benign lesions.[20] Malignant transformation or behavior, including sarcomatous or carcinomatous transformation, has been reported in few subjects.[21]

Recently, 4 patients with local recurrence of MEST and dismal clinical course have been reported.[15,22] A patient with MEST displaying malignant transformation to a sarcomatoid carcinoma with heterogonous components was reported by Shen and colleagues.[22]

Epidemiology and Clinical Features

In a study by Montironi and colleagues, the mean age of the patients with MEST was reported to be 46 years, with the female to male ratio of 6 to 1.[14] Mixed epithelial and stromal tumors were found incidentally in 25% of the subjects with the prevalence of 0.20% to 0.28% of all the renal tumors.[23] According to a study by Shiraishi and coworkers, the mean age for diagnosis of adult MN (more than 15 years old) was 38.2 years (range, 19 to 66 years), and the tumor tended to occur more commonly in women with a male to female ratio of 7 to 15.[9]

In 2000, Nakano and colleagues reviewed a total of 38 adult subjects with MN.[24] Another study on 22 patients with adult MN showed that the patients were predominantly women (20 subjects), with the age range of 19 to 78 years, who were asymptomatic (5 subjects) or had nonspecific signs and symptoms referable to a renal mass. Twenty tumors were classified as classic and 2 as cellular.[13]

We searched MEDLINE and collected reported cases of MEST since 1997 (Table 1). Of 90 patients with MEST, 7 subjects were men and 83 were women, with the mean age of 56 years (range, 17 to 84 years). Eighty-one patients (90%) had benign MEST, whereas in 9 subjects (10%) it was malignant.

Mixed epithelial and stromal tumors do not show distinctive clinical features; therefore, they can not be diagnosed before operation. There are no reports showing that MESTs can be diagnosed from other renal cystic and partially cystic lesions, such as RCC, with imaging modalities.

Presenting signs and symptoms of MEST include flank mass, flank pain, hematuria, or symptoms of urinary tract infection. The most common presenting symptoms are flank mass (31.8%) and gross hematuria (27.3%). Flank pain (22.7%)

Table 1. Reported cases of adult mesoblastic nephroma in the literature (from 1997 to 2009)

First author	Number of cases	Year of report
Gemechu T[25]	1	1997
Truong LD[13]	22	1998
Matias Garcia JJ[30]	1	1998
Shiraishi K[9]	1	1999
Yani H[31]	1	2000
Nakano M[24]	1	2000
Kumar N[32]	1	2000
Tejido Sanchez A[33]	1	2001
Roy PG[34]	1	2002
Bisceglia M[35]	2	2003
Michal M[11]	22	2004
Nakagawa T[36]	2	2004
Groves AM[37]	1	2004
Yap YS[38]	1	2004
Battisti S[39]	1	2004
Moch H[40]	1	2004
Alatassi H[41]	1	2005
Comperat E[42]	1	2005
Seike K[43]	1	2006
Rauf F[44]	1	2006
Ekici AL[15]	1	2006
Chou HP[45]	1	2006
Kwon JE[16]	1	2007
Torres Gomez FJ[46]	1	2007
Sharma JB[47]	1	2007
Agarwal R[48]	1	2007
Sukov WR[49]	1	2007
Buritica C[50]	1	2007
Gupta G[51]	1	2007
Moslemi MK[12]	1	2008
Jung SJ[52]	2	2008
Sireci AN[53]	1	2008
Colombo P[54]	1	2008
Sangoi AR[55]	1	2008
Mohd Zam NA[56]	3	2009
Large MC[57]	1	2009
Tsuchiyama K[58]	1	2009
Xiang H[59]	5	2009
Terao H[23]	1	2009
Total of cases	**90**	

is recognized frequently. The diameter of the tumor was comparatively large and more than 5 cm (mean, 12.3 cm) in all except 5 reported cases. Most MN tumors occur around the upper pole of the kidney.[6] Until 1998, only 22 cases of adult MN were reported in the English literature. After that, 7 cases have been added.[13,25]

Adult MN displays a distinctive morphologic spectrum similar to its pediatric counterpart. The collecting duct differentiation expressed by most tubules and cysts of adult MN implies the ureteric bud, which is the exclusive embryologic origin of the collecting duct, as an important element in the histogenesis of this rare, but fascinating type of tumor. Differentiation is necessary from atypical MN, which shows aggressive behavior.[13,26] Interestingly, MN almost exclusively affects adult women, with the mean age of 56 years (range, 20 to 71 years). Patients can be asymptomatic, or they can present with abdominal pain or discomfort.

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis of adult MN is RCC. The latter carries a significantly poorer prognosis and may need more radical treatment. The RCC is variable in appearance and far more abundant. A complete list of differential diagnosis is presented in Table 2.

DIAGNOSIS

Mesoblastic nephroma may present as a large (range, 4 to 8 cm), unilateral renal mass with nodular density, or as diffuse renal enlargement on ultrasonography. These tumors are predominantly solid, but cystic areas are occasionally seen.[27] Although there is little documentation of the imaging appearances of adult MN, there has been a brief review of computed tomography features. Most of these tumors appear as solid masses with homogenous attenuation on unenhanced sequences. The tumors tend to enhance heterogeneously after injection of intravenous contrast medium. There has been no evidence of associated venous abnormalities or lymphadenopathy in all the cases, demonstrating benign nature of these neoplasms.[9]

Table 2. Differential diagnoses[14]

Cystic partially differentiated nephroblastoma
Multilocular cystic renal cell carcinoma
Angiomyolipoma with epithelial cysts
Synovial sarcoma of the kidney
Metanephric adenofibroma
Renal cell carcinoma surrounded by angiomyolipoma
Renal cell carcinoma associated with prominent angioleiomyoma-like proliferation
Sarcomatoid carcinoma with heterologous elements
Teratoma

According to the study by Sahni and colleagues,[28] all MESTs of the kidney appeared as well-marginated, multi-septate cystic masses with a nodular component. All lesions were classified as Bosniak category III or IV. The presence of calcification or a capsule was variable. Although the possibility of MN due to its rareness is never considered in adults, but the radiologist should be aware of its occurrence, especially in asymptomatic patients with no associated venous abnormality or lymphadenopathy. Mixed epithelial and stromal tumor of the kidney has a diverse radiographic appearance, indistinguishable from multilocular cystic nephroma and cystic RCC. Fine needle aspiration may have a role in the diagnosis of MN pre-operatively.[26]

TREATMENT

Mixed epithelial and stromal tumor of the kidney is probably a benign tumor that can be treated successfully by complete excision.[13] At the time of nephrectomy, the safety margin is necessary because MN shows fingerlike spread into the surrounding tissues.[29] Mixed epithelial and stromal tumor of the kidney has been treated successfully by radical or partial nephrectomy or by tumorectomy alone.[13] None of the reported patients was put on any adjuvant chemotherapy or radiotherapy.

PROGNOSIS

Rare and unusual morphologic features of MESTs have been reported. Although an aggressive behavior has been reported in very few cases, but in general, MESTs are benign and surgical excision is curative. After total or partial nephrectomy without adjuvant chemotherapy or radiotherapy, 19 patients, including the 2 subjects with cellular MN, were alive and well at 8-month to 48-year follow-up. One case had recurrence at the surgical site 24 years after nephrectomy.[13] Only one patient of a total of 22 reported subjects by Truong and associates[13] and also the reported case by Moslemi [12] have recurred. Local recurrence is due to extensions into the adjacent tissues, making a complete surgical removal impossible.[13] Although adult MN appears to be a benign tumor, documentation of more cases will contribute to an understanding of its clinical behavior.

CONCLUSION

Until the past decade, mixed epithelial and stromal tumors were called as adult mesoblastic nephroma, but this term is still used inadvertently that should be discarded.[12,34,43,46] The most important aspect is the occasional cases reported with malignant transformation to sarcoma[12] or carcinoma,[60] which pose the dilemma of their being actual malignant transformations.[14] Therefore, in every patient with MEST, malignant transformation should be borne in mind. It is important to consider the possibility of this tumor when encountering cases of cystic tumor in middle-aged and older women and men with a previous history of estrogen administration.

CONFLICT OF INTEREST

None declared.

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