Int J Clin Exp Pathol 2016;9(2):2599-2605
www.ijcep.com /ISSN:1936-2625/IJCEP0018311

Case Report

Renal angiomyolipoma with epithelial cysts: report of a rare cystic variant of angiomyolipoma and review of the literature

Li-Jun Wan[1], Qi Zhang[2], Pei-Ying Hu[3], Ming Zhao[4]

[1]Department of Urology, Quzhou People's Hospital, Quzhou 32400, China; [2]Department of Urology, Zhejiang Provincial People's Hospital, Hangzhou 310014, China; [3]Department of Health Promotion Center, Zhejiang Provincial People's Hospital, Hangzhou 310014, China; [4]Department of Pathology, Zhejiang Provincial People's Hospital, Hangzhou 310014, China

Received October 22, 2015; Accepted December 22, 2015; Epub February 1, 2016; Published February 15, 2016

Abstract: Angiomyolipoma with epithelial cysts (AMLEC), or cystic AML, is a recently characterized, distinctive cystic subtype of AML of the kidney. To date, less than two dozen of such case have been reported. Herein, we reported a prototypical case of AMLEC occurring in a 41-year-old female patient who presented with left low back pain for one month. Abdominal computed tomograph scan demonstrated a well-demarcated, 2.5-cm complex cystic mass in the mid-pole of left kidney which abutted renal capsule and protruded into perirenal fat. Laparoscopic tumorectomy was performed. Histologically, the tumor was composed of three components. The first component was multiple cysts lined by cuboidal to columnar epithelial cells. The second component was a compact layer of subepithelial "cambium-like" condensation composed of short-spindled to small round stromal cells. The third component was a thick exterior wall of plump smooth muscle cells that arranged in poorly formed fascicles, appearing to emanate from thick-walled, dysplastic blood vessels. Immunohistochemically, the subepithelial stromal cells showed strong and diffuse reactivity to antibodies against HMB45, melan A and CD10, and patchy reaction to antibodies against smooth muscle actin (SMA) and desmin. The exterior smooth muscle cells strongly and diffusely expressed SMA and desmin and occasionally expressed HMB45, melan-A and CD10. Both subepithelial stroma and exterior smooth muscle cells showed strong and diffuse nuclear labeling for ER and PR. The epithelium lining the cystic spaces labeled strongly with PAX8, AE1/AE3 and CK7, but not with melanocytic markers or hormone receptors. The patient has been alive with no evidence of disease for 8 months postoperatively. We summarize the clinicopathologic features of this usual variant of AML with an emphasis on differential diagnosis based on literature review.

Keywords: Angiomyolipoma, epithelial cysts, kidney, differential diagnosis

Background

Renal angiomyolipoma (AML) is a mesenchymal neoplasm composed of variable proportions of dysmorphic blood vessels, spindle and epithelioid smooth muscle-like cells, and mature adipose tissue [1]. Although regarded initially as a hamartomatous nonneoplastic overgrowth of native renal tissues, AML has currently been shown to be a true neoplasm [2]. There is a growing body of literature indicating that AML demonstrates perivascular epithelioid cell (PEC) differentiation and therefore belongs to the PEComa tumor family, which also includes lymphangiomyomatosis, clear cell "sugar" tumor of the lung and pancreas, and a group of rare, morphologically, and immunohistochemically similar lesions seen in other sites [3, 4]. Several histologic subtypes have been described in renal AML including those showing predominance of one of the three components, such as muscle predominant-AML, adipose predominent-AML and vessels predominant-AML, as well as those showing abundant inflammatory infiltration and prominent epitheliod cell morphology, named inflammatory subtype and epithelioid subtype, respectively [5-7]. Recently, an unusual cystic variant of renal AML characterized by smooth muscle-predominent AML with epithelial cysts formation has been recognized and was termed angiomyolipoma with epithelial cysts (AMLEC) by Fine

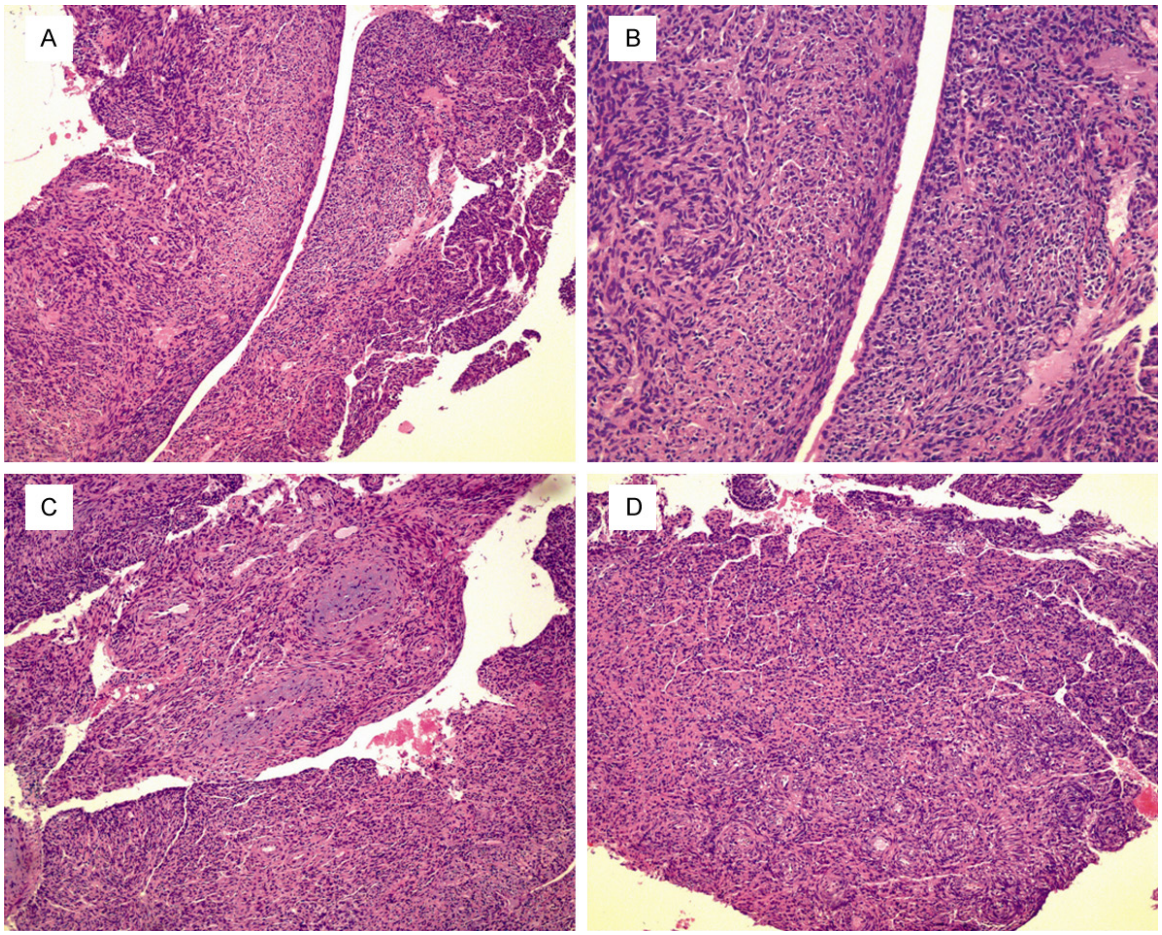

Figure 1. Renal angiomyolipoma with epithelial cysts (AMLEC) consisted of three components: (A, B) (1) epithelial cysts lined by cuboidal to hobnail cells; (2) a compact subepithelial "cambium-like" layer of cellular, Mullerian-like stroma; and (3) muscle-predominant AML with associated thick-walled, dysmorphic blood vessels (C) exterior to the cellular subepithelial stroma. (D) Areas showed that the smooth muscle bundles were dissected by branching and curvilinear spaces, yielding a strong resemblance to lymphangiomyomatosis.

and colleagues [8] or cystic angiomyolipoma by Davis and colleagues [9] in 2006. From then on, less than two dozen of this AML subtype have been documented in the English language literature to date [10-14]. Because most renal AMLs are solid tumors both grossly and microscopically, they generally do not enter into the differential diagnosis of adult cystic renal neoplasms. However, AMLEC may significantly cause diagnostic confusions with adult cystic renal neoplasms that include mixed epithelial and stromal tumor (MEST), cystic nephroma (CN), synovial sarcoma (SS) [15] and renal angiomyoadenomatous tumor (RAT) [16]. We report herein a further example of AMLEC and summarize the clinicopathologic features of this unusual variant of AML with an emphasis on differential diagnosis based on literature review.

Case presentation

In October 2013, a 41-year-old female patient was incidentally found to have a small left-kidney mass on abdominal ultrasonography for routine medical examination at an outside hospital. She was asymptomatic without any treatment of the mass. One year later the occurrence of left low back pain which persisted for one month led the patient to seek assistance in our hospital for urologic surgery. She had no personal or family history of the tuberous sclerosis complex (TSC), renal cyst, renal malignance, or estrogen hormonal exposure. The abdominal computed tomograph (CT) scan demonstrated a well-demarcated, 2.5-cm complex cystic mass in the mid-pole of left kidney that abutted renal capsule and protruded into perirenal fat without penetration into the under-

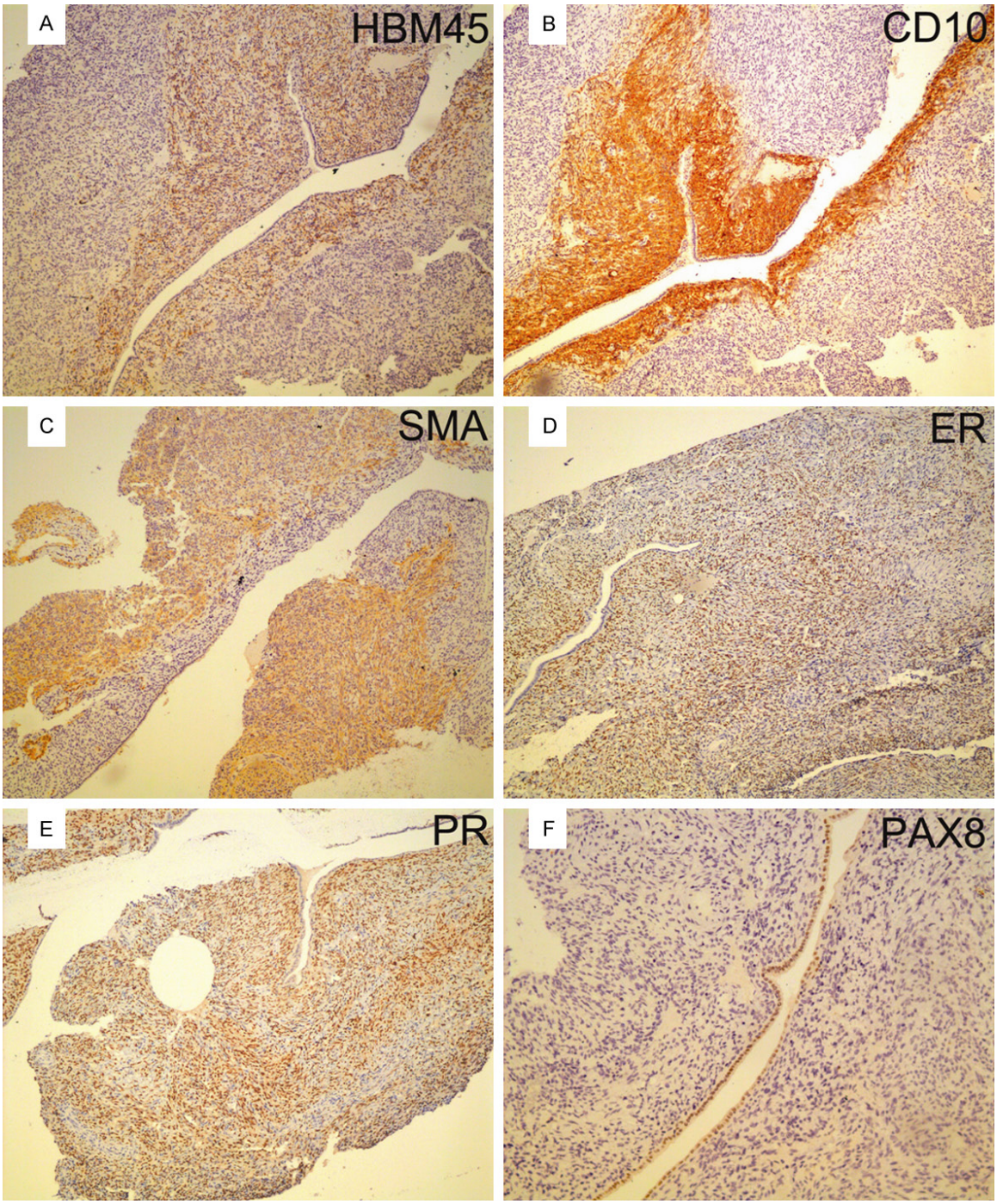

Figure 2. Immunohistochemically, the subepithelial "cambium-like" stromal cells showed strong and diffuse reaction to antibodies against HMB45 (A), melan A, and CD10 (B), and patchy reaction to antibodies against SMA (C) and desmin. The exterior smooth muscle cells strongly and diffusely expressed SMA (C) and desmin and occasionally expressed HMB45 (A), melan-A and CD10 (B). Both subepithelial stroma and exterior smooth muscle cells showed strong, diffuse nuclear labeling for ER (D) and PR (E). The epithelium lining the cystic spaces expressed strongly PAX8 (F).

lying intrarenal cortex, otherwise the contralateral kidney was unremarkable. The radiological impression favored a benign lesion but could not exclude the possibility of a cystic renal cell carcinoma (RCC). Thus, the woman underwent a right laparoscopic tumorectomy. Both the

intraoperative impression and the postoperative CT scan confirmed that gross-total tumor resection had been achieved. Her recovery was uneventful, and there was no evidence of local recurrence or metastasis from the tumor 8 months after surgery.

Materials and methods

The resection specimen was fixed in 10% buffered formalin. Tissue sections were routinely processed and stained with hematoxylin and eosin. Immunohistochemical analysis was performed using avidin-biotin-complex immunoperoxidase technique with a panel of commercially available primary antibodies to the following antigens: cytokeratin AE1/AE3 (AE1/3, Dako), cytokeratin 7 (CK7) (OV-TL12/30, Dako), CD10 (56C6, Dako), renal cell carcinoma marker (RCCma) (gp200, Dako), PAX8 (polyclonal, Proteintech), inhibin-α (R1, Dako), D2-40 (D2-40, Dako), smooth muscle actin (SMA) (1A4, Dako), desmin (D33, Dako), estrogen receptor (SP1, Dako), progesterone receptor (PgR 636, Dako), melan-A (A103, Dako), HMB45 (HMB45, Dako) and Ki67 (MIB-1, Dako). Appropriate positive and negative controls were run concurrently for all the markers tested.

Results

Grossly, the resected specimen was composed of multiple grey to yellow, cystic tissue fragments measuring 3.0 cm in aggregate greatest dimension, with the largest cyst measuring up to 0.9 cm. The entire tumor was submitted for histological assessment. Microscopic examination revealed no normal renal parenchymal structures present within the lesion; the tumor was composed of three components (**Figure 1A-D**). The first component was multiple cysts lined by cuboidal to columnar epithelial cells that contained moderate pale-to-eosinophilic cytoplasm and bland nuclei. The second component was a compact layer of subepithelial "cambium-like" condensation composed of short-spindled to small round stromal cells with indistinct cytoplasm. The third component was a thick exterior wall of plump smooth muscle cells with eosinophilic to focally clear cytoplasm that arranged in poorly formed fascicles, often appearing to emanate from thick-walled, dysplastic and tortuous blood vessels. Areas showed that the smooth muscle bundles were dissected by branching and curvilinear spaces, yielding a strong resemblance to lymphangiomyomatosis. The third component was typical of muscle-predominent AML. There were no fat tissues present within the lesion.

Immunohistochemically, the subepithelial "cambium-like" stromal cells showed strong and diffuse reaction to antibodies against HMB45 (**Figure 2A**), melan A and CD10 (**Figure 2B**), patchy reaction to antibodies against SMA and desmin. The exterior smooth muscle cells showed reverse immunoreactive pattern to that of subepithelial "cambium-like" stromal cells, they strongly and diffusely expressed SMA (**Figure 2C**) and desmin, and occasionally expressed HMB45, melan-A and CD10. Both subepithelial stroma and exterior muscle-predominent AML showed strong and diffuse nuclear labeling for ER (**Figure 2D**) and PR (**Figure 2E**). The epithelium lining the cystic spaces labeled strongly with PAX8 (**Figure 2F**), AE1/AE3 and CK7, but not with melanocytic markers (HMB45 and Melan A) or hormone receptors (ER and PR). D2-40 labeled the branching and curvilinear spaces between the smooth muscle bundles thus confirmed there lymphatic nature. Ki67 labeled less than 1% lesional cells. Inhibin-α and RCCma did not label any of the elements of the tumor.

Discussion

Renal AMLs that demonstrate cystic change of various degree usually due to tumor necrosis or intralesional hemorrhage, is not uncommon, particularly for those larger tumors. However, AMLs with true cysts formation defined by epithelial cells lining the cystic spaces are rare and only have occasionally been mentioned in the literature, as they were initially reported by Fine *et al.* [8] and Davis *et al.* [9] in 2006. AMLEC has recently been officially recognized as a distinct cystic subtype of AML by *International Society of Urological Pathology* (ISUP) Vancouver Classification of Renal Neoplasia in 2012 [17].

Clinically, AMLECs usually present as slow-growing, asymptomatic, partially cystic masses and are detected incidentally by radiographic investigations for other unrelated reasons. However, larger tumors may present as nonspecific urologic symptoms such as flank pain and gross hematuria. AMLECs display a female predominance affecting female population twice

as frequently as male population, patients typically have no history of estrogen hormonal exposure [8, 9, 11]. It is well known that AMLs occur both in the setting of TSC and sporadically, and the occurrence of bilateral or multiple AMLs has been considered presumptive evidence of TSC. Although most AMLECs occur without the background of TSC, a recent study by Adyin *et al.* [4] suggested that TSC associated AMLs showed much more frequently epithelial cysts histology corresponding to AMLEC than non-TSC associated AMLs, thus, identification of epithelial cysts in AMLs should raise the suspicion for TSC in these patients.

Histologically, AMLECs have characteristic features and consist of three components: (1) epithelial cysts lined by cuboidal to hobnail cells; (2) a compact subepithelial "cambium-like" layer of cellular, Mullerian-like AML stroma with prominent admixed chronic inflammation; and (3) muscle-predominant AML with associated dysmorphic blood vessels exterior to the cellular subepithelial stroma. Immunohistochemically, the tumor labels with HMB-45 and melan-A most intensely in the cellular subepithelial stroma, whereas expression of smooth muscle actin and desmin demonstrates the opposite pattern, with greatest intensity in the peripheral muscle-predominant AML areas. Immunoreactivity for ER, PR and CD10 shows the strongest and most diffusely staining in the subepithelial AML cells. Epithelial cells were labeled diffusely with PAX2/8 but not with melanocytic markers or hormone receptors [17].

With regard to differential diagnosis, AMLEC should be distinguished from a variety of adult cystic renal neoplasms that feature both epithelial cysts and stromal components, which include MEST, CN, SS and RAT. MEST, previously classified as cystic hamartomas of the renal pelvis, adult mesoblastic nephroma, or renal pelvic hamartomas, is the entity most closely overlaps with AMLEC [14, 18, 19]. Histologically, both lesions are composed of cystic epithelial and mesenchymal components in variable distribution, the stroma of both tumors can contain mullerian-type element and smooth muscle fibers. Furthermore, by immunohistochemical analysis, the stroma of both tumors expresses SMA, desmin, ER, and PR. However, several differences between MEST and AMLEC are apparent on the basis of the published case studies. Clinically, MEST occurs predominantly in females with patients often having a long-term history of estrogen exposure before the tumor is detected [19]. This clinical picture is dissimilar to that of AMLEC which shows only a slight female predilection, with none patient having a significant history of exogenous hormone exposure. Histologically, in contrast to the lining epithelia of AMLEC which usually display a single layer of flat, low cuboidal, or hobnail cells, the epithelial elements of MEST can demonstrate a complex architecture of glands, tubules, cysts and papillae that are lined by flatted, cuboidal, columnar cells, urothelium, and rarely ciliated cells [17]. The smooth muscle fibers of MEST have deeply eosinophilic cytoplasm and usually arrange in well-formed fascicles, contrasting to those of AMLEC which have more epithelioid and clear cytoplasm and typically form less well-developed fascicles dissected by lymphatic channels [9]. Finally, the vessels of MEST do not show the dysplastic features of those of AMLEC, such as variable thickness and disorganization. Importantly, the most distinctive feature of AMLEC to distinguish from MEST, is immunostaining with melanocytic markers HMB-45, Melan A, or Cathepsin K [20]. CN may possess cuboidal or hobnail epithelium lining similar to that in AMLEC; however, it occurs predominantly in females, and is generally characterized by thin septa with hypocellular ovarian-type stroma and lacks the thick muscular wall vessels seen in AMLEC [8]. In fact, CN and MEST are considered as variations of the same lesion by 2012 ISUP Vancouver Classification [17], due to their significant similarities in clinicopathologic and genetic features [19].

Other adult cystic renal tumors that may enter into the differential diagnosis of AMLEC are primary renal SS [15] and RAT [16]. Both tumors contain cystic epithelium and spindle-shaped or smooth muscle-like stroma causing diagnostic confusions with AMLEC, particularly if provided with a tiny of needle biopsy materials. However, these tumors will be ready excluded if careful attention is drawn to the characteristic morphologic features of AMLEC, together with the aid of immunohistochemical stain to confirm its melanocytic differentiation.

The histogenesis of AMLEC is unclear. The mullerian-like stroma in AMLEC has been postulated to be due to the embryological proximity

between the urinary and genital systems [8]. The mullerian histomorphology and peculiar immunohistochemical profile (HMB45+, Melan-A+, ER+, PR+, and CD10+) of the subepithelial stromal cells suggest both mullerian and melanocytic differentiation of PECs in AMLEC. This observation of dual differentiation is not unprecedented in AML, since the smooth muscle cells of AMLs are known to have both melanocytic and muscular features. The minimal immunoreactivity for muscle markers in this subepithelial zone suggests that these cells have lost some of their muscular phenotype while developing a mullerian phenotype [8]. Whether the epithelial cysts within AMLEC represent entrapped renal tubules or a constitutive part of the tumor is controversial. Some investigators favored the former view [8] while others favored the latter [9, 11, 14]. However, a recent study by Karafin *et al.* [21] showed that the lining epithelia in AMLEC expressed PAX2 and PAX8 but not ER or PR, as our case has illustrated, this finding together with their prior study of the morphologic similarities between cystic epithelium of AMLEC and distal convoluted tubule promoted these authors to suggest that the epithelial cysts of AMLEC represent entrapped distal renal tubules that undergo cystic transformation due to irritation of undetermined local factors.

Conclusion

In summary, AMLEC should be routinely included in the differential diagnostic considerations for adult cystic renal neoplasms that feature both epithelial cysts and mesenchymal components, which include MEST/CN, SS and RAT. Careful attention should be drawn by surgical pathologists to the characteristic morphologic features of AMLEC, together with the aid of immunohistochemical staining to confirm its melanocytic differentiation, to avoid misdiagnosis.

Acknowledgements

This work was supported by Medicine and Health Research Foundation of Zhejiang Province (Grant No. 2015106257), Science and Technology Agency Research Foundation of Zhejiang Province (Grant No. 2013C33204), and China National Natural Science Foundation (Grant No. 81502541). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in Chief of this Journal.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ming Zhao, Department of Pathology, Zhejiang Provincial People's Hospital, 158 Shangtang Road, Xiacheng District, Hangzhou 310014, Zhejiang, PR China. Tel: +86-571-85893289; Fax: +86-571-85893289; E-mail: zhaomingpathol@163.com

References

[1] L'Hostis H, Deminiere C, Ferriere JM and Coindre JM. Renal angiomyolipoma: a clinicopathologic, immunohistochemical, and follow-up study of 46 cases. Am J Surg Pathol 1999; 23: 1011-1020.

[2] Cheng L, Gu J, Eble JN, Bostwick DG, Younger C, MacLennan GT, Abdul-Karim FW, Geary WA, Koch MO, Zhang S and Ulbright TM. Molecular genetic evidence for different clonal origin of components of human renal angiomyolipomas. Am J Surg Pathol 2001; 25: 1231-1236.

[3] Pan CC, Chung MY, Ng KF, Liu CY, Wang JS, Chai CY, Huang SH, Chen PC and Ho DM. Constant allelic alteration on chromosome 16p (TSC2 gene) in perivascular epithelioid cell tumour (PEComa): genetic evidence for the relationship of PEComa with angiomyolipoma. J Pathol 2008; 214: 387-393.

[4] Aydin H, Magi-Galluzzi C, Lane BR, Sercia L, Lopez JI, Rini BI and Zhou M. Renal angiomyolipoma: clinicopathologic study of 194 cases with emphasis on the epithelioid histology and tuberous sclerosis association. Am J Surg Pathol 2009; 33: 289-297.

[5] Sun K, Zhao M, Yao H, Wang L and Wei J. Premelanosome-negative inflammatory angiomyolipoma of liver with expression of cathepsin K and TFE3. Int J Clin Exp Pathol 2014; 7: 8170-8175.

[6] Nese N, Martignoni G, Fletcher CD, Gupta R, Pan CC, Kim H, Ro JY, Hwang IS, Sato K, Bonetti F, Pea M, Amin MB, Hes O, Svec A, Kida M, Vankalakunti M, Berel D, Rogatko A, Gown AM and Amin MB. Pure epithelioid PEComas (so-called epithelioid angiomyolipoma) of the kidney: A clinicopathologic study of 41 cases: detailed assessment of morphology and risk stratification. Am J Surg Pathol 2011; 35: 161-176.

[7] Shimada S, Harada H, Ishizawa K and Hirose T. Retroperitoneal lipomatous angiomyolipoma associated with amyloid deposition masquerading as well-differentiated liposarcoma. Pathol Int 2006; 56: 638-641.
[8] Fine SW, Reuter VE, Epstein JI and Argani P. Angiomyolipoma with epithelial cysts (AMLEC): a distinct cystic variant of angiomyolipoma. Am J Surg Pathol 2006; 30: 593-599.
[9] Davis CJ, Barton JH and Sesterhenn IA. Cystic angiomyolipoma of the kidney: a clinicopathologic description of 11 cases. Mod Pathol 2006; 19: 669-674.
[10] Armah HB, Yin M, Rao UN and Parwani AV. Angiomyolipoma with epithelial cysts (AMLEC): a rare but distinct variant of angiomyolipoma. Diagn Pathol 2007; 2: 11.
[11] Mikami S, Oya M and Mukai M. Angiomyolipoma with epithelial cysts of the kidney in a man. Pathol Int 2008; 58: 664-667.
[12] Rosenkrantz AB, Hecht EM, Taneja SS and Melamed J. Angiomyolipoma with epithelial cysts: mimic of renal cell carcinoma. Clin Imaging 2010; 34: 65-68.
[13] Acar T, Harman M, Sen S, Kumbaraci BS and Elmas N. Angiomyolipoma with epithelial cyst (AMLEC): A rare variant of fat poor angiomyolipoma mimicking malignant cystic mass on MR imaging. Diagn Interv Imaging 2015; 96: 1195-8.
[14] Mai KT, Elkeilani A and Veinot JP. Mixed epithelial and stromal tumour (MEST) of the kidney: report of 14 cases with male and PEComatous variants and proposed histopathogenesis. Pathology 2007; 39: 235-240.
[15] Schoolmeester JK, Cheville JC and Folpe AL. Synovial sarcoma of the kidney: a clinicopathologic, immunohistochemical, and molecular genetic study of 16 cases. Am J Surg Pathol 2014; 38: 60-65.
[16] Aron M, Chang E, Herrera L, Hes O, Hirsch MS, Comperat E, Camparo P, Rao P, Picken M, Michal M, Montironi R, Tamboli P, Monzon F and Amin MB. Clear Cell-Papillary Renal Cell Carcinoma of the Kidney Not Associated With End-stage Renal Disease: Clinicopathologic Correlation With Expanded Immunophenotypic and Molecular Characterization of a Large Cohort With Emphasis on Relationship With Renal Angiomyoadenomatous Tumor. Am J Surg Pathol 2015; 39: 873-888.
[17] Srigley JR, Delahunt B, Eble JN, Egevad L, Epstein JI, Grignon D, Hes O, Moch H, Montironi R, Tickoo SK, Zhou M, Argani P and Panel IRT. The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia. Am J Surg Pathol 2013; 37: 1469-1489.
[18] Turbiner J, Amin MB, Humphrey PA, Srigley JR, De Leval L, Radhakrishnan A and Oliva E. Cystic nephroma and mixed epithelial and stromal tumor of kidney: a detailed clinicopathologic analysis of 34 cases and proposal for renal epithelial and stromal tumor (REST) as a unifying term. Am J Surg Pathol 2007; 31: 489-500.
[19] Zhou M, Kort E, Hoekstra P, Westphal M, Magi-Galluzzi C, Sercia L, Lane B, Rini B, Bukowski R and Teh BT. Adult cystic nephroma and mixed epithelial and stromal tumor of the kidney are the same disease entity: molecular and histologic evidence. Am J Surg Pathol 2009; 33: 72-80.
[20] Martignoni G, Bonetti F, Chilosi M, Brunelli M, Segala D, Amin MB, Argani P, Eble JN, Gobbo S and Pea M. Cathepsin K expression in the spectrum of perivascular epithelioid cell (PEC) lesions of the kidney. Mod Pathol 2012; 25: 100-111.
[21] Karafin M, Parwani AV, Netto GJ, Illei PB, Epstein JI, Ladanyi M and Argani P. Diffuse expression of PAX2 and PAX8 in the cystic epithelium of mixed epithelial stromal tumor, angiomyolipoma with epithelial cysts, and primary renal synovial sarcoma: evidence supporting renal tubular differentiation. Am J Surg Pathol 2011; 35: 1264-1273.