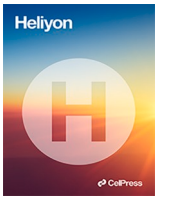
Heliyon 10 (2024) e34191

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Case report

TSC1 splicing mutation in renal angiomyolipoma with epithelial cysts without fat: A very rare case report and literature review

Qiushi Xu [a,b,1], Liying Yin [a,1], Juan Tao [a,**], Fang Peng [a,*]

[a] Department of Pathology, The Second Affiliated Hospital of Dalian Medical University, Dalian, 116027, Liaoning, China
[b] Department of Neurosurgery, Dalian Municipal Central Hospital, Central Hospital of Dalian University of Technology, Dalian, 116003, Liaoning, China

ARTICLE INFO

Keywords:
Angiomyolipoma
Epithelial cysts
No fat
TSC
Case report

ABSTRACT

Renal angiomyolipoma is a benign mesenchymal tumor that can be divided into classical and other subtypes. Angiomyolipoma with epithelial cysts (AMLEC) is an extremely rare non classical subtype. AMLEC without fat component is even rarer. We report a case of AMLEC without fat in a 29-year-old man who was provisionally diagnosed with cystic renal carcinoma by ultrasonography, abdominal enhanced CT and MRI. He had no complaints, or personal or family history of TSC, or other malignancies. Based on imaging findings, robot-assisted laparoscopic nephron-sparing partial nephrectomy through a retroperitoneal approach was performed for the purpose of both diagnosis and treatment. We diagnosed AMLEC after considering the differential diagnosis of other cystic renal neoplasms, such as cystic renal carcinoma, multilocular cystic renal cell neoplasm of low malignant potential, adult cystic nephroma and mixed epithelium and stromal tumor. Meanwhile, the whole-exon sequencing (WES) results showed insert-splicing mutation in the 21st exon and 20th exon of the TSC1 gene. No treatments were performed after the operation and no evidence of recurrence or metastasis at regular follow-up.

1. Introduction

Angiomyolipoma (AML), which accounts for 1 % of surgically resected renal tumors, is a common benign mesenchymal tumor composed of abnormal thick-walled blood vessels, smooth muscle and adipose tissue in varying proportions [1]. It is usually diagnosed by detecting the high fat content using ultrasonography (US), computed tomography (CT) or magnetic resonance imaging (MRI) [2]. AMLEC, an exceptionally rare subtype of AML, is characterized by multilocular cysts, usually with poor or no adipose tissue. AMLEC may be very difficult to be recognised by preoperative imaging findings. AMLEC was first reported in two case series in 2006 [3,4]. To date, less than 30 cases of renal AMLEC have been reported in 10 publications [5–10]. Here we report a rare case of AMLEC in a 29-year-old man.

* Corresponding author. Department of Pathology, The Second Affiliated Hospital of Dalian Medical University, Dalian, 116027, China.
** Corresponding author.
E-mail addresses: blktj09@163.com (J. Tao), pengfanglisa@163.com (F. Peng).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2024.e34191
Received 1 February 2024; Received in revised form 29 June 2024; Accepted 4 July 2024
Available online 6 July 2024
2405-8440/© 2024 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

2. Case presentation

A 29-year-old man was detected with a cystic lesion of the left kidney two years ago, measuring 1.6 cm × 1.3 cm by ultrasonography (US). He had not received any treatment. Two years later, the left renal cystic lesion had grown to 5.3 cm × 5.0 cm by US (Fig. 1A). He was referred to our hospital for further investigation of enlargement mass. The physician considered it as cystic renal carcinoma, which was further favoured by enhanced CT and MRI images (Fig. 1B1–4, Fig. 1C1–8). Physical examination and laboratory tests were unremarkable. He had no complaints, or personal or family history of TSC, or other malignancies. Based on imaging

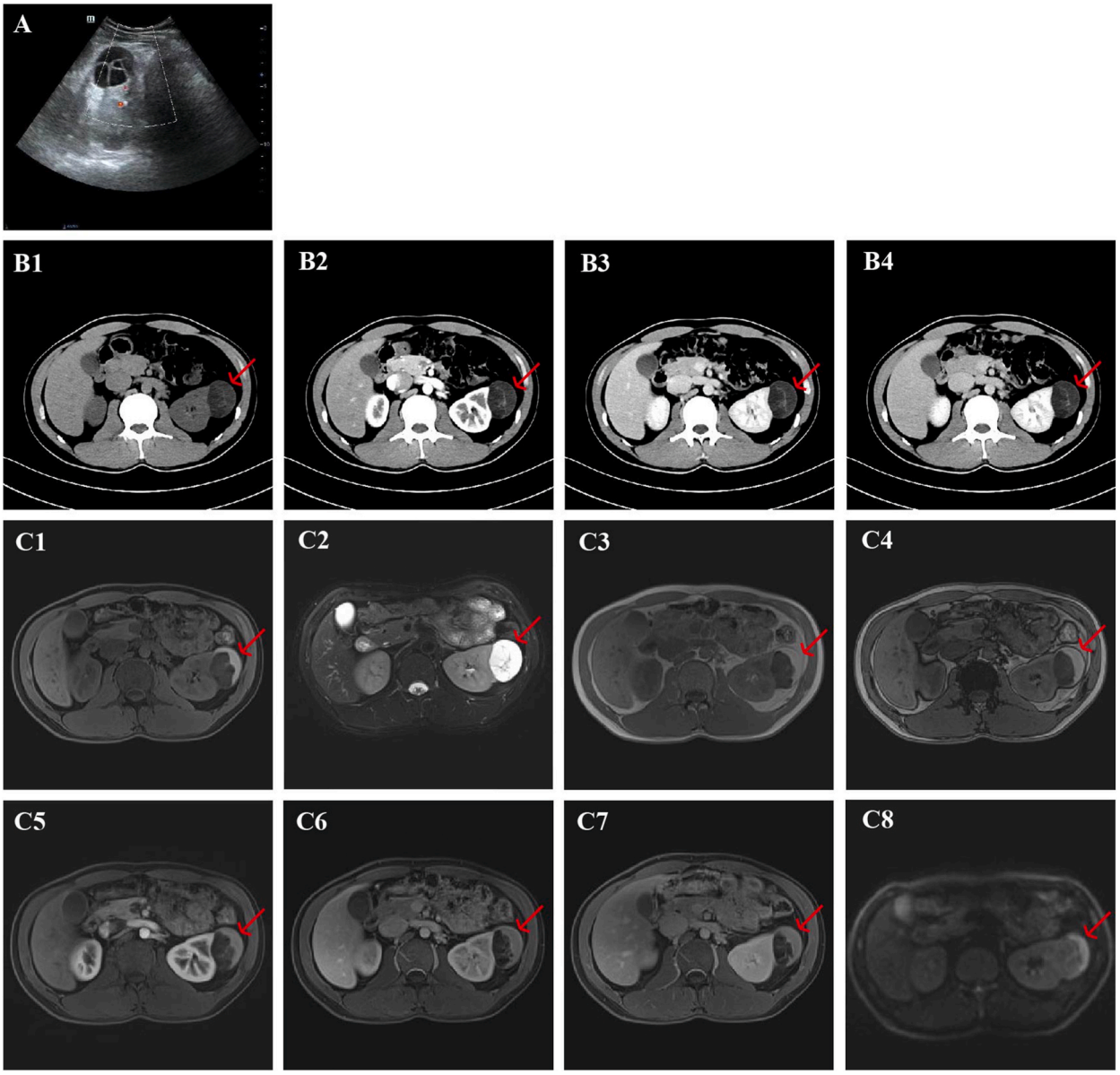


Fig. 1. (A) US revealed an anechoic lesion with clear border, convex outwards, internal segregation and no blood flow signal in the left kidney. (B) Axial CT image showed a partially exophytic cystic lesion (red arrow) measuring 47 mm × 40 mm in the upper pole of the left kidney. There was no enhancement in the cystic portion and slight enhancement in the septum after contrast administration. Unenhanced CT image (B1). Contrast enhanced CT images in cortical phase (B2), medullary phase (B3), excretory phase (B4). (C) A cystic lesion (red arrow) on MRI images. The lesion showed low signal intensity on T1-weighted image and high signal intensity on T2-weighted image, multilocular structures were observed within the lesion. There was no enhancement in the cystic portion and slight enhancement was seen in the septum after contrast administration. Most of the lesion showed isointensity, and the edge was curved hyperintensity on diffusion weighted image (DWI). Axial T1-weighted (C1), axial T2-weighted (C2), axial T1-weighted in-phase (C3), axial T1-weighted out-of-phase (C4). Contrast enhanced MRI images in cortical phase (C5), medullary phase (C6), excretory phase (C7). DWI (C8).

findings, robot-assisted laparoscopic nephron-sparing partial nephrectomy through a retroperitoneal approach was performed.

Grossly, the multicocular cystic tumor was a well demarcated lesion measuring 5.0 cm × 5.0 cm. The cyst wall was grey-white or grey-brown without solid part or fat (Fig. 2A). The tumor mostly protruded outward the perirenal fat. Histologically, the tumor consisted of three components: epithelial cystic regions, subepithelial mesenchymal cell layer, smooth muscle region. Cystic regions were lined by flat, cuboidal or columnar epithelium with eosinophilic or transparent cytoplasm with nuclei. Some of the cells showed a hobnailed appearance (Fig. 2B1); Under the epithelium, there was spindle-shaped cells region. The border of the cells was not clear, resembling ovarian like mesenchymal cells, accompanying with infiltrating lymphocytes and plasma cells (Fig. 2B1–3); Among the spindle-shaped cells, we also observed smooth muscle cells with clear cytoplasm arranged in irregular bundles, appearing to emanate from the thick-walled aberrant blood vessels (Fig. 2B2–3). We didn't find any fatty component in the tumor.

Immunohistochemically, the cyst epithelium was strongly positive for AE1/AE3, CK7 and PAX-8 (Fig. 2C1–3). Subepithelial mesenchymal cells diffusely expressed HMB45, estrogen receptor (ER), progesterone receptor (PR), CD10 and WT1 (Fig. 2C4–8) and patchily expressed melan A, desmin and SMA (Fig. 2C9–11). Smooth muscle cells were positive for desmin and SMA diffusely (Fig. 2C10–11) and HMB45 partially. Ki67 proliferation index was approximately 3 % (Fig. 2C12). Epithelium, subepithelial mesenchymal cells and smooth muscle cells were negative for α-Inhibin (Figure not shown). The whole-exon sequencing (WES) results of the tumor sample showed insert-splicing mutation in the 21st exon and 20th exon of the TSC1 gene (NM_000368: exon 21: c.2626-3- > TTT; NM_001162426: exon 21: c.2623-3- > TTT; NM_001162427: exon 20: c.2473-3- > TTT; NM_001362177: exon 20: c. 2263-3- > TTT). Meanwhile, there was no mutation in the TSC2 gene. Above all, we made the diagnosis of AMLEC, a rare variant of AML. The

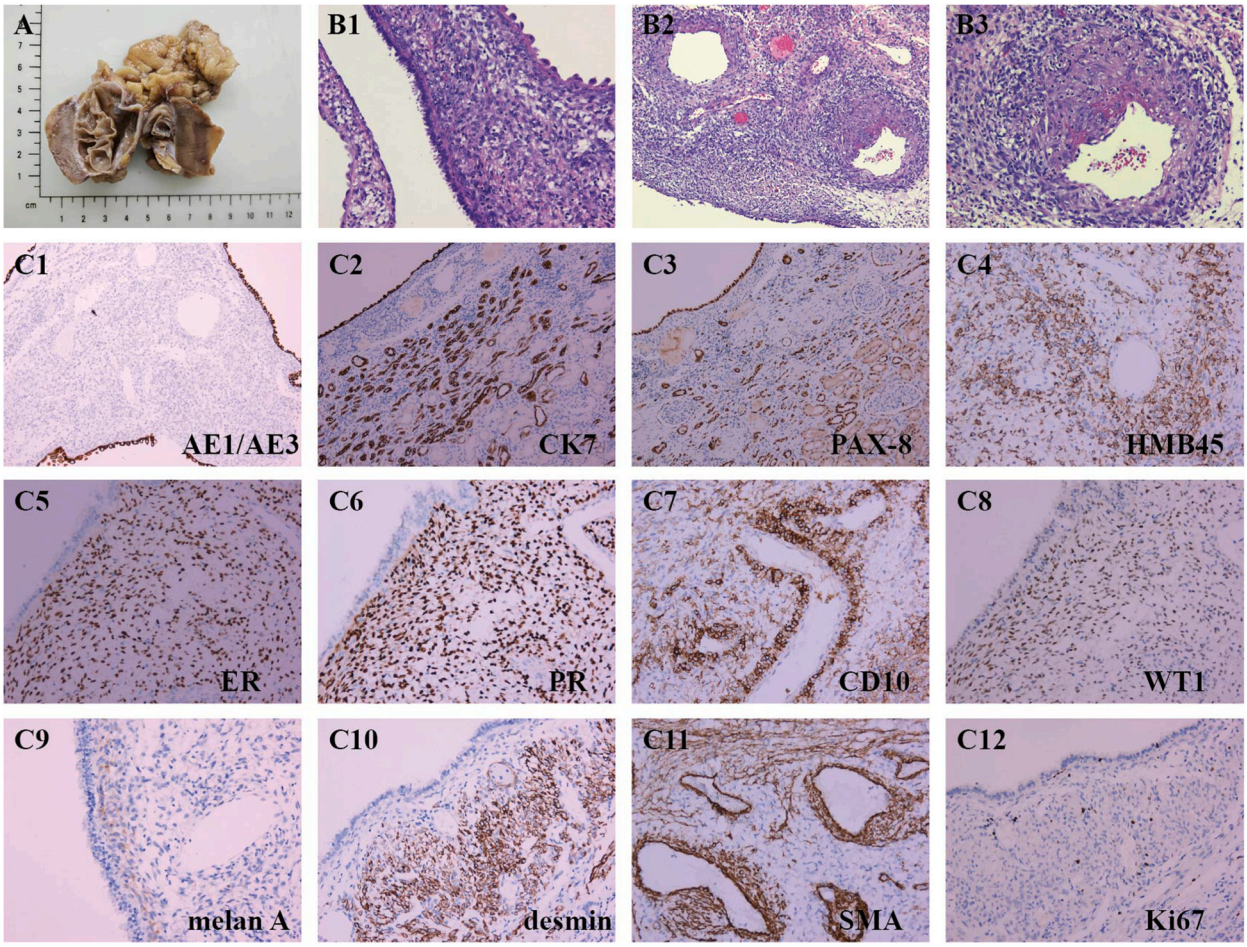


Fig. 2. (A) The tumor with multiple cysts, about 5.0 × 5.0 cm, was well demarcated without solid part or fat on gross examination. (B) Microscopic view of the tumor (hematoxylin-eosin stain, H&E). The cyst wall was thin and covered with flattened, cuboidal, columnar and hobnailed epithelium (B1, × 200 magnification). Dense bands of ovarian-like mesenchymal cells were under the epithelium (B1-2). The subepithelial mesenchymal cell layer, the area of smooth muscle bundles and thick-walled aberrant blood vessels (B2, × 100 magnification; B3, × 200 magnification). (C) Protein labelling of tumor components (immunohistochemical staining, IHC). The cyst epithelium was positive for AE1/AE3, CK7 and PAX-8 (C1-3, × 100 magnification). Subepithelial mesenchymal cells with diffuse expression of HMB45, ER, PR, CD10 and WT1 and patchy expression of melan A, desmin and SMA (C4-11, × 200 magnification). Smooth muscle cells showing diffuse expression of desmin and SMA (C10-11, × 200 magnification). Ki67 proliferation index (C12, × 200 magnification).

patient did not receive treatments after the operation. He recovered well and had no evidence of recurrence or metastasis at the nine-month follow-up with regular abdominal imaging and urological ultrasound test.

3. Discussion

Tuberous sclerosis complex (TSC) is an autosomal dominant hereditary disease caused by inactivating mutations in the TSC1 or TSC2 gene, affecting the brain, kidneys, heart, skin, lung, and so on. There are 60%–80 % of patients with TSC had renal lesions, such as AML, renal cysts and renal cell carcinoma (RCC) [11,12]. AML were detected in 49 % patients with TSC [13]. By contrast, only 8 % AML patients were with TSC [14]. Multiple AMLs or other renal lesions (cysts or RCCs) have been considered as one of clinical diagnosis evidences of TSC. The normal gene result does not exclude TSC, because 10%–25 % of TSC patients identified no gene mutation by conventional genetic testing [12]. In our case, this patient didn't have a family history of this disease and other clinical presentation. We performed the whole-exon sequencing (WES) results of the tumor sample. Insert-splicing mutation in the 21st exon and 20th exon of the TSC1 gene was detected. But it didn't lead to the change of TSC1 amino acid sequences, which implied insert-splicing mutation in TSC1 gene may not the direct etiological factor for AMLEC.

Most TSC patients with renal lesions are asymptomatic [13]. Only a few patients (15 %) have some symptoms, and the most common is haematuria [13]. Approximately 80 % of adult fatalities result from renal hemorrhage due to renal angiomyolipoma (RAML) rupture or nephrological complications. Most AMLs are solid masses on imaging and gross appearance [3], with only a few cases of significant cystic or pseudocystic changes [3–5]. AMLEC is an extremely rare subtype of AML characterized by cysts or epithelial cysts [4,14]. There are only 11 cases with these features of 1064 kidney AMLs at the AFIP [4]. AMLEC was first described in 2006 by Fine et al. and Davis et al. at two research institutions [3,4]. Renal AMLECs occur between the ages of 20 and 70 years (median age 45 years) and are more common in female [4]. Renal AMLEC is asymptomatic in an early small-diameter lesion. But symptoms, such as flank pain, a palpable mass, heamaturia, appear with an increasing tumor diameter [12]. The vast majority of AMLs are isolated solid tumors with rich fat content, which can be diagnosed by CT or ultrasound imaging [2,5,15]. In contrast, the significant cystic AMLECs with very few or no fat mimick as cystic renal cell carcinoma or adult cystic nephroma [15].

In our case, the multilocular tumor protruded outward the perirenal fat with no solid or fat component compared to classic AML. The cyst walls were lined with a single layer of flattened, low cuboidal or columnar epithelial cells, and some areas of the epithelium were hobnailed. These cystic epithelial cells were strongly immunopositively for AE1/AE3, CK7 and PAX-8 proteins. We also found that PAX-8 and CK7 proteins were highly expressed in normal distal kidney tubules. It suggested the cystic epithelial cells in AMLEC may origin from renal tubular, which was consistent with Fine et al. and Karafin et al. [3,16]. However, Davis et al. disagreed with this view [4]. And Filho et al. reported that epithelial cells and the mesenchymal component both can express HMB45 and melan A [8]. Therefore, they favoured the view that the epithelial cells were the result of differentiation of the mesenchymal component of the tumor [4,8]. In AMLECs, the "ovarian-like" cells were strongly positive for HMB-45, which supported they were AML variants. Histomorphology and specific immunohistochemical features (ER+, PR+, $CD10^{+}$, WT1+, HMB45+ and Melan A+) of the dense subepithelial cells suggested both Müller-like and melanocytic differentiation. Meanwhile, smooth muscle cells around the thick-walled vessels expressed both melanocytic and muscular markers, such as HMB45, desmin and SMA. All above these, we made the diagnosis of AMLEC, a rare variant of AML. The low proliferation index of Ki67 also favoured the diagnosis.

When we deal with cystic renal lesions, the following differential diagnosis of AMLEC must be considered: such as multilocular cystic renal cell neoplasm of low malignant potential (MCRN-LMP), adult cystic nephroma (CN) and mixed epithelial and stromal tumor (MEST). However, histopathological examination and immunohistochemistry emerges as the gold standard for the definitive diagnosis.

The main differential diagnostic consideration for AMLEC is MCRN-LMP, called multilocular cystic RCC in the past WHO version. MCRN-LMP shows an entirely cystic architecture, with thin fibrous or hyalinized septa lined by a single layer of flat, cuboidal epithelium, and scattered small blood vessels [17]. The fibrous or hyalinized septa is negative for HMB45, estrogen receptor (ER), progesterone receptor (PR) and WT1 by immunohistochemical staining. Adult cystic nephroma (CN), predominately in females, can be identified by histo-morphology. CN shows a multilocular architecture with absence of communication between the cyst and the renal tissue, and no communication between the multilocular structures [18]. Although AMLEC and adult NC exhibit numerous overlapping immunohistochemical phenotypes, the utilization of HMB45 and Melan A can effectively discriminate between the two entities. They are positive for AMLEC, instead of adult NC. In addition, mixed epithelial and stromal tumor (MEST) consists of spindle cell mesenchyme, glands and cysts [19]. Clinically, MEST tends to occur in women with a long history of estrogen exposure [19]. But it is negative for melanocytic markers such as HMB-45 and Melan A [19,20].

No recurrence or metastasis was found in AMLEC. For asymptomatic patients with renal AMLEC or other classic AML, measuring less than 4cm, morphological evaluation should be conducted using renal US, abdominal CT, or MRI every year [21]. Symptomatic AMLEC more than 4 cm was recommended to perform surgical removal or selective arterial embolization, in order to prevent tumor hemorrhage or rupture [21,22]. Physicians can perform nephrectomy or partial nephrectomy when malignant tumors couldn't be excluded [12]. The everolimus is weakly recommended for renal AMLEC related to TSC [12].

4. Conclusions

Angiomyolipoma with epithelial cysts (AMLEC) is an extremely rare subtype of AML, AMLEC without fat is even rarer. AMLEC without fat has confusing imaging, distinct histomorphological and immunophenotypic features. AMLEC consists of three components: epithelial cystic region, subepithelial mesenchymal cell layer, smooth muscle region. Splicing mutation in TSC1 gene may not a direct

etiological factor for AMLEC in this case. This tumor is benign and with no recurrence or metastasis. Symptomatic AMLEC more than 4 cm requires surgical removal or selective arterial embolization to prevent tumor hemorrhage or rupture.

Ethics statement

This study adhered to the Declaration of Helsinki. The patient willingly gave written informed consent to participate in the study.

Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

CRediT authorship contribution statement

Qiushi Xu: Writing – original draft. **Liying Yin:** Investigation, Formal analysis. **Juan Tao:** Validation, Supervision, Methodology. **Fang Peng:** Writing – review & editing, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors would like to thank the members of their research group for their valuable contributions to the discussions. The authors would also like to thank Juan Tian from the Department of Radiology, Second Affiliated Hospital, Dalian Medical University for providing the imaging images and Jiabei He from the Department of Ultrasound, Second Affiliated Hospital, Dalian Medical University for providing the ultrasound images.

References

[1] H. Moch, P.A. Humphrey, T.M. Ulbright, V.E. Reuter, World Health Organization Classification of Tumors Pathology and Genetics of Tumors of the Urinary System and Male Genital Organs, IARC Press, Lyon, 2016.
[2] B.R. Lane, H. Aydin, T.L. Danforth, M. Zhou, E.M. Remer, A.C. Novick, et al., Clinical correlates of renal angiomyolipoma subtypes in 209 patients: classic, fat poor, tuberous sclerosis associated and epithelioid, J. Urol. 180 (2008) 836–843.
[3] S.W. Fine, V.E. Reuter, J.I. Epstein, P. Argani, Angiomyolipoma with epithelial cysts (AMLEC): a distinct cystic variant of angiomyolipoma, Am. J. Surg. Pathol. 30 (2006) 593–599.
[4] C.J. Davis, J.H. Barton, I.A. Sesterhenn, Cystic angiomyolipoma of the kidney: a clinicopathologic description of 11 cases, Mod. Pathol. 19 (2006) 669–674.
[5] H.B. Armah, M. Yin, U.N. Rao, A.V. Parwani, Angiomyolipoma with epithelial cysts (AMLEC): a rare but distinct variant of angiomyolipoma, Diagn. Pathol. 2 (2007) 11.
[6] M.A. Gorin, S.P. Rowe, M.E. Allaf, P. Argani, Angiomyolipoma with epithelial cysts: add one to the differential of cystic renal lesions, Int. J. Urol. 22 (2015) 1081–1082.
[7] S. Mikami, M. Oya, M. Mukai, Angiomyolipoma with epithelial cysts of the kidney in a man, Pathol. Int. 58 (2008) 664–667.
[8] J.E.P. Filho, D.M. Amorim, G.M.M. Sweet, L.A.R. Freitas, P.R.F. Athanazio, D.A. Athanazio, Renal epithelioid angiomyolipoma with epithelial cysts: demonstration of Melan A and HMB45 positivity in the cystic epithelial lining, Ann. Diagn. Pathol. 16 (2012) 397–401.
[9] J. Wei, Y. Li, Y. Wen, L. Li, R. Zhang, Renal angiomyolipoma with epithelial cysts: a rare entity and review of literature, Int. J. Clin. Exp. Pathol. 8 (2015) 11760–11765.
[10] A. Wood, F. Young, M. O'Donnell, Angiomyolipoma with epithelial cysts masquerading as a cystic renal cell carcinoma, Curr. Urol. 9 (2017) 209–211.
[11] A. Limavady, M. Marlais, Nutritional status as a predictive factor for paediatric tuberous sclerosis complex-associated kidney angiomyolipomas: a retrospective analysis, Eur. J. Pediatr. 183 (2024) 2563–2570.
[12] T. Osawa, M. Oya, T. Okanishi, R. Kuwatsuru, H. Kawano, Y. Tomita, Clinical Practice Guidelines for tuberous sclerosis complex-associated renal angiomyolipoma by the Japanese Urological Association: summary of the update, Int. J. Urol. 30 (2023) 808–817.
[13] J.A. Cook, K. Oliver, R.F. Mueller, J. Sampson, A cross sectional study of renal involvement in tuberous sclerosis, J. Med. Genet. 33 (1996) 480–484.
[14] H. Aydin, C. Magi-Galluzzi, B. R Lane, L. Sercia, J. I Lopez, B.I. Rini, et al., Renal angiomyolipoma: clinicopathologic study of 194 cases with emphasis on the epithelioid histology and tuberous sclerosis association, Am. J. Surg. Pathol. 33 (2009) 289–297.
[15] T. Acar, M. Harman, S. Sen, B.S. Kumbaracı, N. Elmas, Angiomyolipoma with epithelial cyst (AMLEC): a rare variant of fat poor angiomyolipoma mimicking malignant cystic mass on MR imaging, Diagn Interv Imaging 96 (2015) 1195–1198.
[16] M. Karafin, A.V. Parwani, G.J. Netto, P.B. Illei, J.I. Epstein, M. Ladanyi, et al., 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. 35 (2011) 1264–1273.
[17] B. Yang, L. Sun, W.F. Cao, L.S. Qi, Y.H. Guo, Y. Sun, Clear cell renal cell carcinoma with cystic component similar to multilocular cystic renal neoplasm of low malignant potential, Diagn. Pathol. 18 (2023) 27.
[18] R. Verma, J. Verma, N. Gupta, Multilocular cystic nephroma in an adult: a diagnostic quandary, CEN Case Rep. doi: 10.1007/s13730-024-00852-8. Online ahead of print.
[19] N.V. Adsay, J.N. Eble, J.R. Srigley, E.C. Jones, D.J. Grignon, Mixed epithelial and stromal tumor of the kidney, Am. J. Surg. Pathol. 24 (2000) 958–970.
[20] A. Caliò, J.N. Eble, D.J. Grignon, B. Delahunt, Mixed epithelial and stromal tumor of the kidney: a clinicopathologic study of 53 cases, Am. J. Surg. Pathol. 40 (2016) 1538–1549.
[21] J.E. Oesterling, E.K. Fishman, S.M. Goldman, F.F. Marshall, The management of renal angiomyolipoma, J. Urol. 135 (1986) 1121–1124.
[22] K. Yamakado, N. Tanaka, T. Nakagawa, S. Kobayashi, M. Yanagawa, K. Takeda, Renal angiomyolipoma relationships between tumor size, aneurysm formation, and rupture, Radiology 225 (2002) 78–82.