≪Review≫

Review of renal epithelioid angiomyolipoma with focus on clinical and pathobiological aspects

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Abstract :
Epithelioid angiomyolipoma (eAML) is a rare renal neoplasm, in which the proportion of epithelioid cells in eAML accounts for more than 80% of the entire lesion. eAML often occurs with tuberous sclerosis complex as well as a sporadic manner. Histologically, the tumor predominantly consists of epithelioid cells with eosinophilic to clear cytoplasm, frequently showing pleomorphic ganglion-like or multinucleated giant cells. Spindle cells or adipose tissue also proliferate. Perivascular hyalinization and entrapped tubules are frequently identified. Immunohistochemically, neoplastic cells usually show the positivity for melanoma-related antigen (HMB45, HMB50, CD63, and Melan A), and alpha-smooth muscle actin. Ultrastructurally, epithelioid cells contain striated, rhomboid, spherical or elliptical granules which may mimic melanosome, renin granules or rarely form typical premelanosomes. Approximately 40 % of cases with eAML behaves aggressively. As the investigation on indicators of clinical behavior is not enough to date, the accumulation and further examination of cases with eAML is required in the near future.

Keywords : epithelioid angiomyolipoma, kidney, pathology

INTRODUCTION

Renal angiomyolipoma (AML) is composed of various proportions of thick-walled blood vessels, smooth muscle and adipose tissue.[1-4] This lesion has been for a long time considered to be a hamartoma, but is now regarded as a tumor.[5,6] Eble et al. has propose the entity of renal epithelioid AML (eAML) which predominantly consists of epithelioid smooth muscle cells.[7] However, the ratio of epithelioid cells in eAML varies from 10% to 100%, depending on the definition of reported papers.[7-15] The biological behavior of eAML is also quite variable.[7-15] In this article, we review eAML with focus on clinical and pathological aspects.

DEFINITION

According to the recent World Health Organization Classification, eAML is a rare variant of AML and

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the ratio of epithelioid cells in eAML is defined as more than 80% of total neoplasm.[16]

EPIDEMIOLOGY

eAML is often associated with tuberous sclerosis complex, but may occur also in sporadic fashion.[4,7,8] eAML accounts for 4.6% of all AMLs.[12]

CLINICAL SYMPTOMS

Patients generally present with pain, hematuria, mass and fever. Some tumors are incidentally found.1 In cases of association with tuberous sclerosis complex (TSC), symptoms are caused by involvements of organs other than the kidney (seizure due to cortical tuber, dyspnea due to pulmonary lymphangiomyomatosis, facial angiofibroma and mental retardation).

IMAGING FINDINGS

The contrast computed tomography (CT) scan examination of eAML generally reveals a solid hypervascular tumor with homogenous or heterogenous enhancement.[17] The predominant enhancing pattern is rapid wash-in to slow wash-out.[17]

PATHOLOGICAL FINDINGS
MACROSCOPIC FINDINGS

The tumor shows well-demarcated and solid mass. The cut surface of the tumor shows tan, grey or pink color with occasional hemorrhage or necrosis. [7, 18]

MICROSCOPIC FINDINGS

The tumor predominantly consists of epithelioid cells (Fig.1a). Pleomorphic ganglion-like or multinucleated giant cells are frequently observed (Fig. 1b).[4,12] In some cases, spindle cells or adipose tissue proliferate.[10,12] Perivascular hyalinization is often noted (Fig.1c).[12] Entrapped tubules are frequently identified. [4,9] Mitotic activity is variable. [4,9] Atypical mitoses may be seen in some cases (Fig.1d). [4,9] Necrosis is observed in a half of cases.[4,9,10] Tumor thrombus formation may be present in some cases.[13] Melanin deposition may be observed in some cases.[19,20] Sclerosing change is occasionally seen.[10,21] eAML with extensive rhabdoid features is also reported.[21] Oncocytoma-like eAML has been described.[15] Conventional AMLs, including capsuloma may be observed in the nonneoplastic renal parenchyma and the contralateral kidney. Composite renal cell carcinoma may be rarely seen.[22,23]

IMMUNOHISTOCHEMICAL FINDINGS

Immunohistochemically, tumor cells are usually positive for Melanoma-related antigen (HMB45, HMB50 and CD63)(Fig.2a), Melan A, muscle specific actin and alpha-smooth muscle actin (Fig.2b).[24-28] Tyrosinase or epithelial markers including epithelial membrane antigen (EMA), low and high molecular weight cytokeratins are generally negative in most cases.[24-28] E-cadherin show the frequent positivity.[29] Bcl-2, estrogen and progesterone receptors, placental alkaline phosphatase, c-kit and CD68 may be positive in some cases.[28] The Ki-67 labeling index is generally less than 10%, but may exceed 10% in some cases.[30] Strong nuclear positivity for p53 may be observed in some cases.[30]

UITRASTRUCTURAL FINDINGS

Epithelioid cells contain striated, rhomboid, spherical or elliptical granules. These granules may mimic melanosome, renin granules. The presence of needle- and rod-like crystalloid has been reported in epithelioid smooth muscle cells.[2]

MOLECULAR GENETIC FINDINGS

The allelic loss of chromosome 16p13.3 haboring *TSC2* gene region and/or germ-line mutation of *TSC1* or *TSC2* are observed in eAML with tuberous

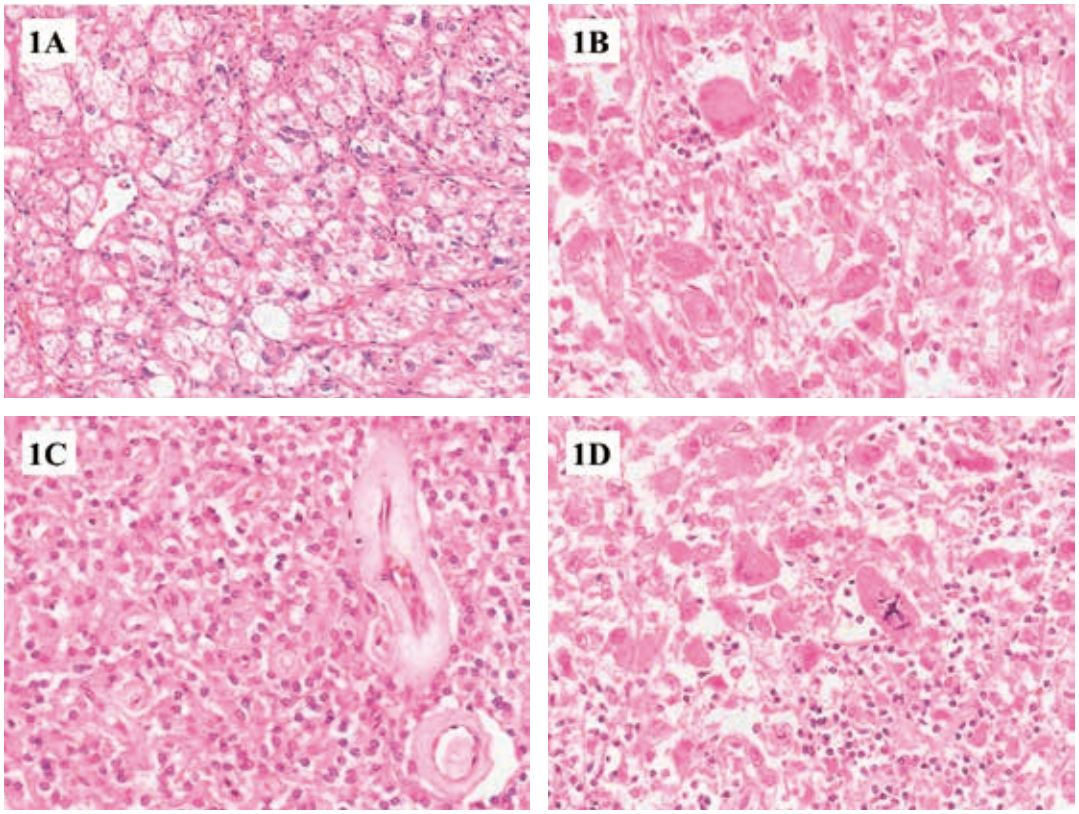

FIG 1. Histological findings. (A) The tumor is composed of epithelioid cells. (B) Multinucleated giant cells are observed. (C) Perivascular hyalinization is observed. (D). Atypical mitotic figure is seen.

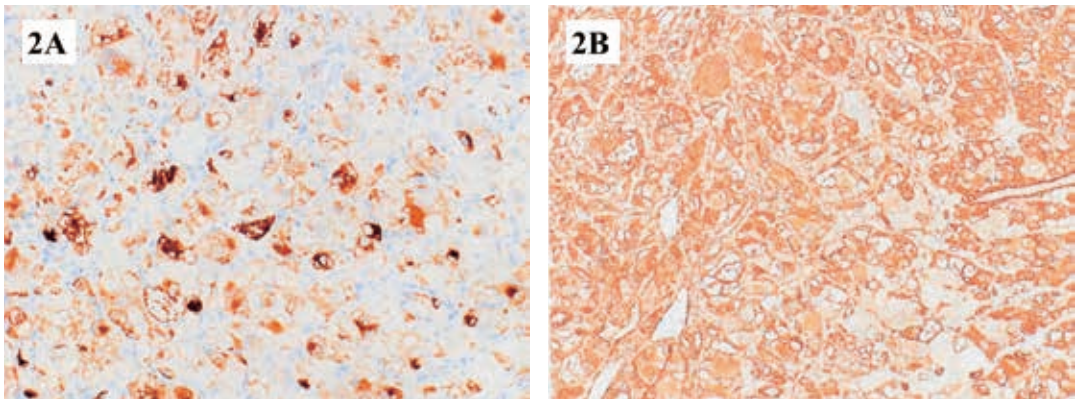

FIG 2. Immunohistochemical findings. Neoplastic cells demonstrate the positivity for Melanosome-related antigen (HMB45) (A) and alpha smooth muscle actin (B).

sclerosis complex[33] Loss of heterozygosity of *TSC2* gene is also identified in sporadic eAML.[25,33] The mutation of the *p53* gene was identified in one case.[30] The *TFE3* gene fusions may be observed in some cases.[31,32]

DIFFERENTIAL DIAGNOSIS

The distinction from clear cell RCC, Xp11.2 translocation-associated RCC (Xp11.2 RCC) and RCC associated with t(6;11) (t(6;11) RCC) is very important. In clear cell RCC, the tumor consists of clear cells with abundant glycogen and lipids, showing alveolar or acinar growth pattern. Thin-walled blood vessels regularly proliferate among neoplastic cells.[34,36] In TSC, it is no so easy for pathologists to distinguish clear cell RCC from eAML. If AML looks like clear cell RCC, it could be

an eAML. In Xp11.2 RCC, the tumor is composed of mixed clear and eosinophilic cells with frequent voluminous cytoplasm. Psammoma bodies or hyaline nodules are often observed in the stroma.[36] Besides the most commonly seen morphology, Xp11.2 RCCs can be arranged in mostly solid pattern and composed of cells resembling urothelial ca, other can produce subnucleolar vacuoles (*TFE3-NONO*) or quite recently, cases with predominantly clear cell population were associated with pseudorosette formation. Neoplastic cells of t(6;11) RCC are composed of tumor cells of two different sizes, namely larger and smaller cells, and basement membrane materials are surrounded by the latters, resulting in pseudorosettes formation.[37]

THERAPY

Radical or partial nephrectomy has been previously performed in most cases. Arteriographic embolization may be a feasible therapeutic option.[38] In tumors with metastatic disease, chemotherapy including doxorubicin or cisplatin, immunotherapy such as interferon, radiotherapy or molecular targeted therapy (sunitinib, sorafenib, axitinib, everolimus) were tried.[25,38,39,44] Considering loss of function *TSC1* and/or *TSC2*-encoding proteins (hamartin and/or tuberin, respectively) suppressing the mTOR pathway, inhibitors of mTOR pathway are hopeful for unresectable diseases.

PROGNOSIS

Approximately 40 % of cases with eAML behaves in an aggressive fashion.[33,37-45] Nese et al. investigated the clinicopathologic parameters that may be associated with disease progression, which include tuberous sclerosis complex or concomitant AML, necrosis, tumor size>7cm, extrarenal extention and/or renal vein involvement and carcinoma-like growth pattern. According to this report, the biological behavior was divided into three categories, namely low, intermediate, and high risk for disease progression which met zero to one, or two to three, or four to five adverse prognostic parameters, respectively. The low, intermediate and high risk categories showed the disease progression in 15%, 65% and 100% of all cases, respectively.[10] Lei et al. indicated that a close follow-up is necessary for cases having 1) tumor size>9cm, 2) tumor thrombus formation in the vein, 3) epithelioid cells >70% or atypical cells >60%, or 4) necrosis.[13]

FUTURE PERSPECTIVES

There are few reports on the clinical and pathological difference between eAML with and without *TFE3* gene arrangement.[32] Therefore, to elucidate the difference between these diseases is very important. Furthermore, to clarify the clinical indicators in eAML is also crucial. As the investigation on indicators of clinical behavior is not enough to date, the accumulation and further examination of cases with eAML is required in the near future.

DISCLOSURE STATEMENT

None declared.

REFERENCES

1 Helene L, Colette D, Jean-Marie F, et al. Renal angiomyolipoma: A clinicopatholgic, immunohistochemical and follow-up study of 46 cases. Am J Surg Pathol. 1999; 23: 1011-20.
2 Tamboli P, Ro JY, Amin MB, et al. Benign tumors and tumor-like lesions of the adult kidney part II: Benign mesenchymal and mixed neoplasms, and tumor-like lesions. Adv Anat Pathol. 2000; 7: 47-66.
3 Zavala-Pompa A, Folpe AL, Jimenez RE, et al. Immunohistochemical study of Microphthalmia transcription factor and tyrosinase in angiomyolipoma of the kidney, renal cell carcinoma, and renal and peritoneal sarcoma. Comparative evaluation with traditional diagnostic markers. Am J Surg Pathol. 2001; 25: 65-70.
4 Aydin H, Magi-Galluzzi C, Lane BR, et al. Renal angiomyolipoma. Epithelioid histology and tuberous

sclerosis association. Am J Surg Pathol. 2009; 33: 289-97.
5 Paradis V, Laurendeau I, Vieillefond A, et al. Clonal analysis of renal sporadic angiomyolipoma. Hum Pathol. 1998; 29: 1063-7.
6 Kattar MM, Grignon DJ, Eble JN, et al. Chromosomal analysis of renal angiomyolipoma by comparative genomic hybridization: evidence for clonal origin. Hum Pathol. 1999; 30: 295-9.
7 Eble JN, Amin MB, Young RH. Epithelioid angiomyolipoma of the kidney. A report of five cases with a prominent and diagnostically confusing epithelioid smooth muscle component. Am J Surg Pathol. 1997; 21: 1123-30.
8 Pea M, Bonetti F, Martignoni G, et al. Apparent renal cell carcinomas in tuberous sclerosis are heterogenous: The identification of malignant epithelioid angiomyolipoma. Am J Surg Pathol. 1998; 22: 180-7.
9 Brimo F, Robinson B, Guo C, et al. Renal epithelioid angiomyolipoma with atypia: A series of 40 cases with emphasis on clinicopathologic prognostic indicators of malignancy. Am J Surg Pathol. 2010; 34: 715-22.
10 Nese N, Martignoni G, Fletcher CD, et al. 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: 161-76.
11 Faraji H, Nguyen BN, Mai KT. Renal epithelioid angiomyolipoma: a study of six cases and a meta-analytic study. Development of criteria for screening the entity with prognostic significance. Histopathology. 2009; 55: 525-34.
12 He W, Cheville JC, Sadow PM, et al. Epithelioid angiomyolipoma of the kidney: pathological features and clinical outcome in a series of consecutively resected tumors. Mod Pathol. 2013; 26: 1355-64.
13 Lei JH, Liu LR, Wei Q, et al. A four-year follow-up study of renal epithelioid angiomyolipoma: A multi-center experience and literature review. Scientific Reports. 5:10030 DOI:10.1038/srep10030.
14 Hornick JL, Fletcher CDM. PEComa: What do we know so far? Histopathology. 2006; 48: 75-82.
15 Martignoni G, Pea M, Reghellin D, et al. PEComas: the past, the present and the future. Virchows Arch. 2008; 452: 119-32.
16 Martignoni G, Reuter VE, Cheville J, et al. Epithelioid angiomyolipoma. In: WHO classification of tumors of the urinary system and male genital organ. 4th Ed. IARC press, Lyon; c2016, 65 p.
17 Liu Y, Qu F, Cheng R, et al. CT-imaging features of renal epithelioid angiomyolipoma. World J Surg Oncol .2015; 13: 280.
18 Cho NH, Shim HS, Choi YD, et al. Estrogen receptor is significantly associated with the epithelioid variants of renal angiomyolipoma: A clinicopathological and immunohistochemical study of 67 cases. Pathol Int. 2004; 54: 510-5.
19 Goyal R, Joshi K, Singh SK, et al. Melanotic clear cell epithelioid angiomyolipoma: a rare entity and a mimic of clear cell renal carcinoma. Histopathology. 2007; 50: 388-404.
20 Adachi S, Hanada M, Kobayashi Y, et al. Heavily melanotic perivascular epithelioid clear cell tumor of the kidney. Pathol Int. 2004; 54: 261-5.
21 Miyai K, Mullick SS, Divatia MK, et al. Renal sclerosing perivascular epithelioid cell tumor (PEComa)/angiomyolipoma with extensive rhabdoid cell features. Pathol Int. 2014; 64: 247-50.
22 Cao QH, Liu F, Xiao P, et al. Coexistence of renal epithelioid angiomyolipoma and clear cell carcinoma in patients without tuberous clerosis. Int J Surg Pathol. 2012; 20: 196-200.
23 Mai KT, Perkins DG, Robertson S, et al. Composite renal cell carcinoma and angiomyolipoma: A study of the histogenetic relationship of the two lesions. Pathol Int. 1999; 49: 1-8.
24 Behnes GL, Schutze G, Engelke C, et al. 13-year-old tuberous sclerosis patient with renal cell carcinoma associated with multiple renal angiomyolipomas developing multifocal micronodular pneumocyte hyperplasia. BMC Clinical Pathology. 2013; 13: 4.
25 Mete O, van der Kwast TH. Epithelioid angiomyolipoma. A morphologically distinct variant that mimics a variety of intra-abdominal neoplasm. Arch Pathol Lab Med. 2011; 135: 665-70.
26 Martignoni G, Pea M, Bonetti F, et al. Carcinomalike monotypic epithelioid angiomyolipoma in patients without evidence of tuberous sclerosis: A clinicopathologic and genetic study. Am J Surg Pathol. 1998; 22: 663-72.
27 Ma L, Kowalski D, Javed K, *et al*. Atypical angiomyolipoma of kidney with a patient with tuberous sclerosis. Arch Pathol Lab Med. 2005; 129: 676-9.
28 Acikalin MF, Tel N, Oner U, et al. Epithelioid angiomyolipoma of the kidney. Int J Urol. 2005; 12: 204-7.
29 Wang Z, Gong Q, Fan Q. Expression of E-cadherin in

angiomyolipoma. Hum Pathol. 2012; 43: 1248-53.
30 Li W, Guo L, Bi X, et al. Immunohistochemistry of p53 and Ki-67 and p53 mutation analysis in renal epithelioid angiomyolipoma. Int J Clin Exp Pathol. 2015; 8: 9446-51.
31 Argani P, Aulmann S, Illei PB, et al. A distinctive subset of PEComas habors TFE3 gene fusions. Am J Surg Pathol. 2010; 34: 1395-406.
32 Ohe C, Kuroda N, Hes O, et al. A renal epithelioid angiomyolipoma/perivascular epithelioid cell tumor with TFE3 gene break visualized by FISH. Med Mol Morphol. 2012; 45: 234-7.
33 Martignoni G, Pea M, Rigaud G, et al. Renal angiomyolipoma with epithelioid sarcomatous transformation and metastases. Demonstration of the same genetic defects in the primary and metastatic lesions. Am J Surg Pathol. 2000; 24: 889-94.
34 Nagashima Y, Kuroda N, Yao M. Transition of organizational category on renal cancer. Jpn J Clin Oncol. 2013; 43: 233-42.
35 Mikami S, Oya M, Mizuno R, et al. Recent advances in renal cell carcinoma from a pathological point of view. Pathol Int. 2016; 66: 481-90.
36 Kuroda N, Mikami S, Pan CC, et al. Review of renal carcinoma associated with Xp11.2 translocations/*TFE3* gene fusions with focus on pathobiological aspect. Histol Histopathol. 2012; 27: 133-40.
37 Kuroda N, Tanaka A, Sasaki N, et al. Review of renal carcinoma with t(6;11)(p21;q12) with focus on clinical and pathobiological aspects. Histol Histopathol. 2013; 28: 685-90.
38 Varma S, Gupta S, Taiwar J, et al. Renal epithelioid angiomyolipoma: a malignant disease. J Nephrol. 2011; 24: 18-22.
39 Cibas ES, Goss GA, Kulke MH, et al. Malignant epithelioid angiomyolipoma ('Sarcoma Ex Angiomyolipoma') of the kidney. A case report and review of the literature. Am J Surg Pathol. 2001; 25: 1121-6.
40 Kawaguchi K, Oda Y, Nakanishi K, et al. Malignant transformation of renal angomyolipoma. A case report. Am J Surg Pathol. 2002; 26: 523-9.
41 Mai KT, Perkins DG, Malignant epithelioid angiomyolipoma. Am J Surg Pathol. 1999; 23: 356-7.
42 Cho SW, Choi HJ, Lee S. Rapidly progressive malignant epithelioid renal angiomyolipoma: A case report. Case Report. 2016; 13: 2653-5.
43 Citak EC, Yilmaz EB, Yaman E, et al. Malignant epithelioid angiomyolipoma of the kidney in a child treated with sunitinib, everolimus and axitinib. Can Urol Assoc. 2015; 9: E542-5.
44 Guo B, Song H, Yue J, et al. Malignant renal epithelioid angiomyolipoma: A case report and review of the literature. Oncol Lett. 2015; 11: 95-8.
45 Qiao LD, Chen S, Tian C, et al. From angiomyolipoma to malignant epithelioid angiomyolipoma of the kidney, a case report with a history of eight years. Int J Clin Exp Pathol .2015; 8: 21252-6.
46 Zheng S, Bi XG, Song QK, et al. A suggestion for pathological grossing and reporting based on prognostic indicators of malignant from a pooled analysis of renal epithelioid angiomyolipoma. Int Urol Nephrol. 2015; 47: 1643-51.