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Synchronous Papillary Thyroid Carcinoma and Renal Epithelioid Angiomyolipoma with Hepatic Metastasis or Concurrence: A Clinicopathological Characteristics and Outcome

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Abstract

The epithelioid angiomyolipoma (EAML) is a variant of angiomyolipoma with predominant epithelioid component which has a potentially malignant behavior. We report a 40-year-old woman with the synchronous renal and hepatic epithelioid angiomyolipoma with preoperative papillary thyroid carcinoma. She had been operated to remove the tumors in her liver and kidney. The histopathological and immunohistochemical results of surgical specimens were concordant with epithelioid angiomyolipoma. Her thyroid carcinoma is still followed up to evaluate. After surgery she had not received any adjuvant therapy. Currently, after 8 months of treatment, she has not appeared with recurrent lesions.

Subject Areas

Diagnostics, Oncology, Pathology

Keywords

EAML, Synchronous, Kidney

1. Introduction

The epithelioid variant of angiomyolipoma (AML) was initially described in the 1990s [1], which comprises 4.6% - 7.7% of all renal operated AMLs [2] [3]. AML originates from mesenchymal tissue and typically consists of three histopathological components: Fusiform spindle or epithelioid smooth muscle cells, dys-

morphic blood vessels and adipose tissue (triphasic pattern). AML may be composed mainly or entirely of one element, such as smooth muscle or adipose tissue. According to the WHO classification, there are two types of renal AML: Classical and epithelioid [4]. So epithelioid angiomyolipoma (EAML) is subgroup of AML which is the less common. The EAML has a predominant epithelioid component and potentially malignant behavior [4] [5]. EAMLs are part of the perivascular epithelioid cell family of tumors (PEComas). They mainly consist of a large number of hyperplastic epithelioid cells arranged in sheets, whereas the proportion of mature fat cells tend to be up to 5%.

In contrast to the benign biological behavior of classic AML, malignant behavior has been observed in some cases of EAML [2] [3] [6] [7]. Characteristics of malignancy, such as the presence of tumor venous extension, distant metastasis and local tumor recurrence have been reported in such EAML cases. EAML is characterized by a predominance of human melanoma black (HMB45+) epithelioid cells [8]. The diagnosis of EAML may be challenging, due to the similarity of its epithelioid morphology with that of renal cell carcinoma [9]. Several cases of EAML metastasized to the liver, lung and bone have been reported in the literature [10] [11]. Therefore, it is important to distinguish EAML from classic AML, as each tumor carries unique therapeutic and prognostic implications. We herein presented the clinicopathological entity and outcome of the first case presented the synchronous renal and hepatic epithelioid angiomyolipoma in Vietnam.

2. Case Presentation

2.1. Clinical Case

Initially, a 40-year-old premenopausal Vietnamese woman was hospitalized with a diagnosis of papillary thyroid carcinoma in the right lobe by the cytological test of fine-needle aspiration under ultrasound guidance. Ultrasonic criteria of the right thyroid were suitable for TIRADS IVa. She didn't have any the personal cancer history.

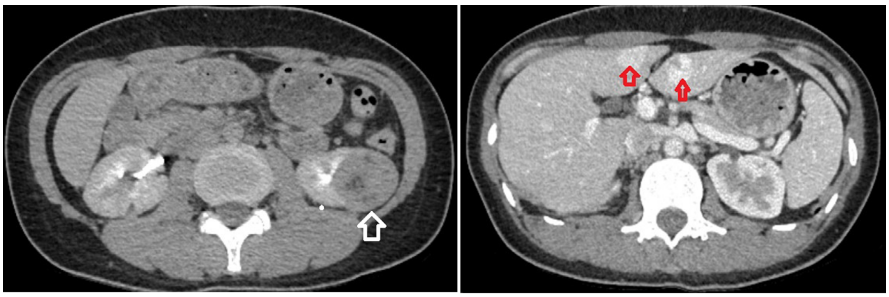
After admission to the hospital, imaging findings such as CT scan, MRI or abdominal ultrasound accidentally showed a mass of the lower pole of the left kidney measuring 45 × 48 mm (**Figure 1(a)**) and 3 nodules in the right kidney up to 15 mm in size. In the lower segments II, IV and VI of the liver, there are masses up to 20 mm, suggesting the metastatic cancer (**Figure 1(b)**). MRI result showed that in the lumbar and sacrum body there were lesions with the largest diameter of 19 mm and bone scintigraphy scan showed that these are benign lesions, not metastases.

2.2. Pathological Features

Afterward, she was taken a punch biopsy for the pre-operated pathological diagnosis. The patient was surgically removed the tumors in the liver and left kidney.

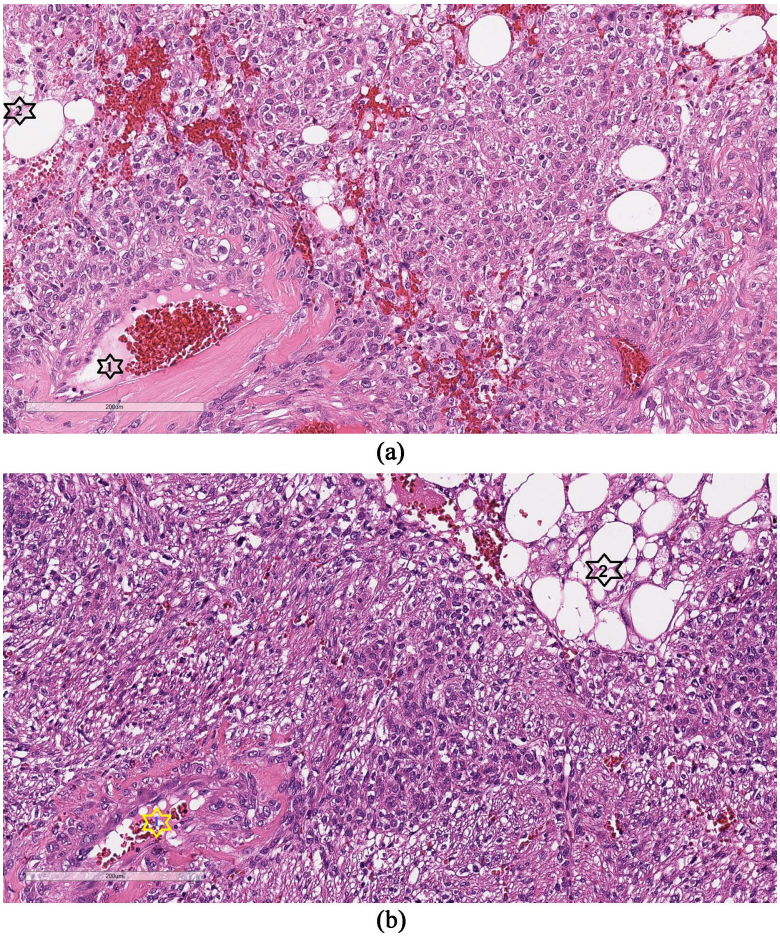
Macroscopically, non-encapsulated tumors had the irregular borders with 5.0 × 5.0 × 3 cm (Kidney), and 1.8 and 1.1 cm (Liver). Cut-surfaces of both hepatic

and renal masses are soft, yellow-brown in color. Microscopically, hematoxylin and eosin staining showed predominantly epithelioid cells with some atypical ones containing abundant clear to eosinophilic granular cytoplasm arranged in nests and sheets. Some bundles of spindle tumor cells are mixed. The cells were unevenly distributed and had pleomorphic nuclei of varying sizes. Both few blood vessels and small foci of mature adipose tissue were trapped (Figure 2(a)



(a) (b)

Figure 1. Illustrated pictures of CT scan showed the renal (black arrow) and hepatic masses (red arrows) ((a) and (b), respectively).



(a)

(b)

Figure 2. Microscopic picture demonstrated the similar histopathological features of renal and hepatic EAML with vascular (the first star), lipocytes (the second stars), and broad sheets of tumoral cell components ((a) and (b), respectively; HE stains, 20×).

and Figure 2(b)). Absence of necrosis and atypical mitosis were appeared in slides.

Immunohistochemically, the tumor cells were negative for PAX8, HepPar-1, Glypican-3, Hepatocyte and CKAE1/AE3 (Figure 3(c)), together with negative for CD117 (c-kit). In contrast, the tumor cells were strong positive for melanocytic markers including human melanoma black 45 (HMB45) (Figure 3(a) and Figure 3(b)), Melan A and Ki-67 labeling index of 5.0%. Accordingly, histopathological results in 2 tumor samples of liver and kidney showed that primary hepatic and renal EAML were diagnosed at that time. According to the proposed

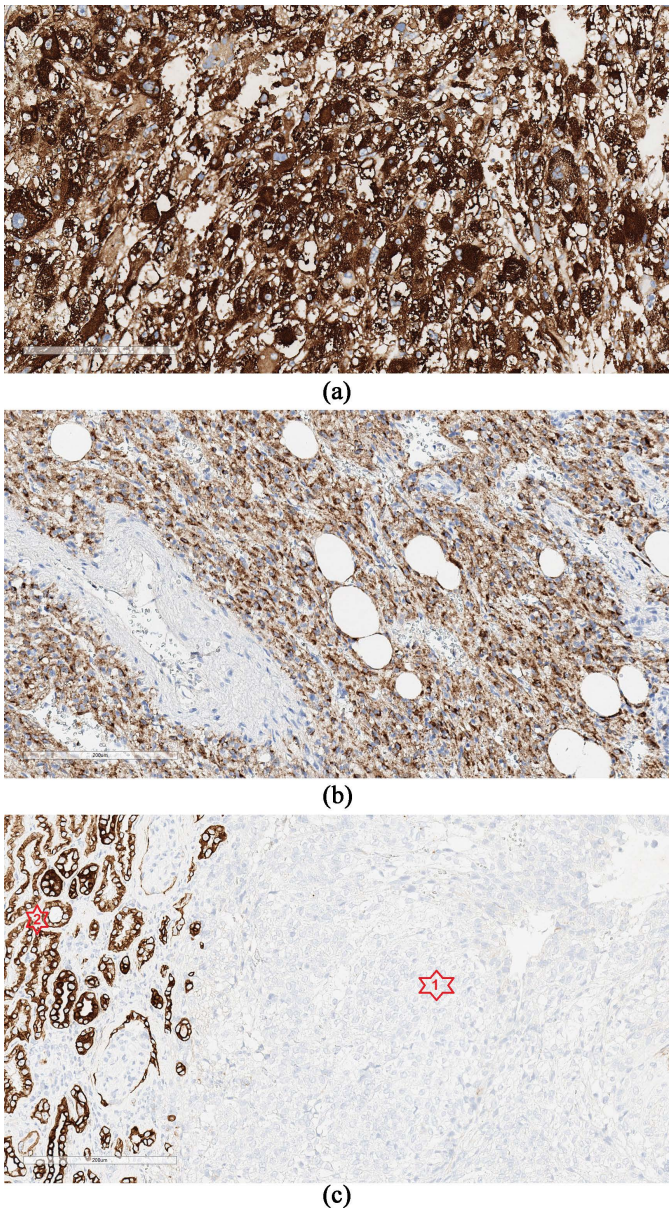


Figure 3. (a) Photomicrographs indicated the strong positive immunohistochemical marker of HMB45 ((a) of renal EMAL and (b) of hepatic EMAL). (c) of pan cytokeratin is negative for tumoral cell components (the first star) and only positive for benign renal epithelial cells (the second star) (IHC stain, 20×).

standards' Yang [12] to make between the differential diagnosis between malignant EAML and benign EAML, this case belongs to the favorable group.

2.3. Treatment and Outcomes

After the nephron-sparing surgery and hepatic lobectomy, she received no adjuvant therapy and she was discharged from the hospital. Currently, after finishing treatment for 8 months, she has not appeared with any recurrent lesions.

3. Discussion

EAML belongs to the microphthalmia associated transcription factor (MiTF) family of tumors. MiTF is involved in melanogenesis. MiT family neoplasms are tumors that harbor gene fusions involving MiT family transcription factors (MiTF, TFE3 and TFEB). Dysregulation of members of the MiTF family has been found to be associated with certain neoplasms such as cutaneous malignant melanoma, clear cell sarcoma of the tendon sheath, and AML, a subset of the family of PEComas [13]. PEComas is a term used for tumors composed of perivascular epithelioid cells (PEC) in various sites, including renal and extrarenal AMLs as hepatic AML, clear cell sugar tumor of the lung, primary extrapulmonary sugar tumor, lymphangiomyomatosis, abdominopelvic sarcoma of PECs, clear cell myomelanocytic tumor, and genitourinary PEComa. AML is most commonly observed in the kidney, followed by the liver. The tumor is thought to originate from pluripotent PECs, although its normal tissue counterpart remains unclear [14] [15].

Histopathologically, focal epithelioid morphology may be observed in a number of classic AMLs. There is no consensus as to the percentage of epithelioid cells required for diagnosing EAML, with some authors [6] [16] suggesting that only ≥ 5% of the cells must exhibit epithelioid histology, while others demanding at least 20% [17] [18] or even 80% [4] [16]. The diagnosis of EAML may be challenging, due to the similarity of its epithelioid morphology with that of renal cell carcinoma [9]. Similarly, Zhong *et al.* reported misdiagnosis of 14 cases as hepatocellular carcinoma [19]. Initially, this patient's liver biopsy fragment was diagnosed histopathologically as hepatocellular carcinoma clear cell type. However, on surgical tissue samples with immunohistochemical staining were confirmed as EAML. Therefore, an awareness of this entity and its characteristic features, including immunoreactivity such as HMB45, may aid its identification. The degree of staining for HMB45 between primary and metastatic lesion. Moreover, a previous investigation showed that lack of c-kit expression is suggestive of malignant hepatic AML [20], in contrast to c-kit immunopositivity in benign lesions [21]. Although further investigation of the intensity of c-kit staining in malignant cases is required, it is potentially a predictive marker.

It is very important to assess the malignant potential of EAML, according to Nese *et al.*'s study [22], the presence of ≥3 of the following factors was highly prognostic for aggressive biological behavior: Presence of tuberous sclerosis

syndrome, tumor size > 7.7 cm, tumor necrosis, extrarenal extension or renal vein invasion and carcinoma-like histopathology. In another series [6], ≥70% of atypical epithelioid cells, >2 mitoses/10 high-power fields, atypical mitoses and necrosis were considered as adverse prognostic factors; the presence of ≥3 of these factors was highly associated with malignant behavior. Bi *et al.* demonstrated that tumor size, necrosis and invasive growth differed significantly between favorable and adverse prognostic groups of renal EAML patients [23]. Meanwhile, Lei *et al.*'s study showed the three progressive cases met the following characteristics concerning to general and pathological features: 1) tumor size > 9 cm, 2) tumor thrombus formation in the vein, 3) epithelioid cells > 70% or atypia cells > 60%, and 4) necrosis. They recommended a lesion met 3 or more of the above features predicted increased risk of malignant behavior and should clinically be closely followed [7]. The combined diagnostic criteria of Lei's and Yang's studies based on histopathology and imaging results are helpful in determining the malignant potential of EAML in practice [7] [12].

We are asking ourselves whether this entity may be just the concurrent masses of multiple organs rather than as a metastatic disease. Following to the previous researches, EAML can occur in different organs: kidney and extrarenal sites, such as liver, pancreas, spleen, uterus, uterine tubes, lips and lymph nodes, etc [19] [24] [25] [26]. Besides the kidney, the liver is the organ more frequently involved by AML, both the classic and the epithelioid types. Marcuzzi *et al.* also reported a case of EAML which were detected in liver and kidney at the same time [25], it is concordant with this patient. Therefore, the concept of metastasis in patients with the synchronous EAML of multiple organs is an issue in order to have to be carefully considered. Because the diagnosis of metastatic EAML was given to the clinical doctors who will affect to make exact decision for treatment and prognosis of the patient with EAML. Initially, our patient was diagnosed with EAML of kidney with liver metastases; however, upon careful examination of histopathological features and immunohistochemistry of tumor samples of liver and kidney we found similarity. Furthermore, Brimo *et al.*'s developed a predictive model of 4 atypical features that included: 1) ≥70% atypical epithelioid cells, 2) ≥2 mitotic figures per 10 hpf, 3) atypical mitotic figures, and 4) necrosis; the presence of 3 or all of the features was highly predictive of malignant behavior [6]. This case was not met any Brimo *et al.*'s criteria. Similarly, according to the proposed standards' Yang, this case belongs to the favorable group. Therefore, according to the pathophysiology of EAML, this tumor can be seen in many organs, along with similarities in pathological and immunohistochemical characteristics, we suggest that, in each particular circumstance, EAML may be named as multi-organ or multi-centric tumor rather than metastatic disease, the same to Azevedo *et al.*'s recommendation [26]. Similarly, the previous studies demonstrated the presence of tumors in extrarenal sites are considered multicentric, not metastatic disease [27] [28] [29]. However, more systematic studies have to be investigated.

The treatment of choice for primary and locally recurrent EAML is surgical resection. However, due to its rarity, there are currently no treatment guidelines for metastatic disease. The malignant potential of renal EAML may result in local recurrence and/or metastatic disease, most frequently to the liver, lymph nodes, lungs and peritoneum [2] [3] [6] [7]. Collective data of a total of 130 EAML patients from various series [3] [7] [6] [22] demonstrated that the median time to local recurrence was 15 months and the median time to lymph node or systemic recurrence was 14 months. Although in one series [22] 33% of the 33 selected renal EAML patients succumbed to the disease, in other such series [2] [3] [7] [22] with similar follow-up periods this rate was significantly lower, with percentages ranging from 0 to 11%. The mortality rate may be slightly higher with longer follow-up, since patients developing late recurrence, as in the present case, have also been reported. In Bree *et al.*'s report, over 52 months follow up. It is noteworthy that the patient remains in excellent clinical condition and free of any symptoms [30]. He *et al.* demonstrated that follow-up data was available on all 20 patients with EAML. Over a mean follow-up of 82.5 months, only one patient (5%) developed distant metastases; 17 were alive with no-evidence-of-disease at the time of last follow-up and two patients died of unrelated causes [3]. After a median follow-up of 52 months only 1 of the 20 patients had developed metastatic disease, while all others remained disease-free. The authors considered that the incidence of malignant behavior of true EAML appeared to be in the order of 5% [16]. Fukuda *et al.*'s case, no hepatic recurrence was observed over nearly 7 years. In 2013, a chest X-ray showed a well-defined nodule in the right lung field, therefore, a diagnosis of lung metastases from hepatic EAML was made. The patient has remained recurrence-free on a closer follow-up schedule for 2 years after pneumonectomy [31].

Considering to the multiple primary malignant tumors (MPMTs), since the first report of Billroth and the definition of Warren and Gates, the number of patients with second malignant neoplasms had progressively increased over time, with new second malignant neoplasms now representing about one in six of all cancers reported to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program [32]. MPMTs are defined as two or more independent primary malignancies of different histologies/origins in the same individual [33]. Warren and Gates defined the criteria for diagnosis of double primary malignancies based on histopathological confirmation of primary and secondary tumors, there should be at least 2 cm of normal mucosa and separated by at least 5 years in time if both tumors in the same location, and the probability of second tumor being metastasis of the primary one must be excluded [34]. The first point that deserves clarification regarding multiple tumors is what does the term "primary" means. Firstly, tumors must be histologically different. Secondly, they must involve different organs. Finally, metastatic lesions among these tumors must be excluded [35]. Double primary malignancies could be divided into two categories, depending on the interval between tumor diagnoses such as synchronous and metachronous neoplasms. Synchronous ma-

lignancies were second tumors which have been occurring either simultaneously, or within 6 months after the first malignancy while metachronous malignancies were secondary tumors that have developed after 6 months, or even more than that from the first malignancy [36]. The tendency of some subjects to develop multiple tumors (synchronous or metachronous) may be explained either by an individual predisposition or by the action of carcinogenic factors acting on different organs at different times [35]. Liu *et al.* demonstrated the prevalence of MPMTs in their study was 0.99% (152/15,398): 51 cases (0.33%) were synchronous, and 101 cases (0.66%) were metachronous [33]. We have also previously reported 1 woman with 2 types of different cancer, however it was the metachronous MPMTs [37]. This case belongs to the synchronous group due to two her neoplasms found at the same times. The incidence rate of other primary neoplasms associated with thyroid cancer reported in the literature is 13.1% for males and 13.7% for females [38] [39]. The occurrence of any type of cancer in patients diagnosed with thyroid cancer is twice as common as in the general population. Gabora *et al.*'s study showed that there are 3 cases of the synchronous thyroid cancer with any type of cancer, including one breast cancer and two malignant melanomas [40].

4. Conclusion

In this respect, we regard the renal and hepatic EAML as a borderline malignant tumor, and they may be the synchronous tumors in the different organs. The aggressive therapeutic intervention is recommended since surgical resection is indisputably the most reliable curative treatment. Due to the rarity, it is challenging to diagnose and determine the most appropriate therapy protocol. The present case suggests that it is crucial for pathologists and/or oncologists to recognize this rare entity.

Statement of Ethics

Ethical approval is not required for this study in accordance with local guidelines. Written informed consent was obtained from the patient for publication of details of her medical case and any accompanying images.

Conflicts of Interest

The authors declare no conflicts of interest.

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