

Hepatic epithelioid hemangioendothelioma with metastasis to the mesentery of the small intestine: A case report

DAICHI NAKAMURA¹, YASUSHI ADACHI², YASUAKI NAKASHIMA³, NORIKO SAKAIDA³⁻⁵, HIROYUKI NARAHARA⁶, MING SHI⁷, MICHIHIKO TSUBONO¹ and SUSUMU IKEHARA⁸

Departments of ¹Surgery and ²Diagnostic Pathology, Toyooka Hospital, Toyooka, Hyogo 668-8501; ³Department of Pathology and Cytology Center, BML Group PCL Japan, Ibaraki, Osaka 567-0865; ⁴Department of Pathology, Osaka City University Graduate School of Medicine, Osaka 545-8586; ⁵Department of Diagnostic Pathology, Kakogawa Central Hospital, Kakogawa, Hyogo 675-8611; ⁶Department of Medical Oncology, Nishinomiya Hospital, Nishinomiya, Hyogo 662-0918, Japan; ⁷School of Public Health, Guangdong Medical University, Dongguan, Guangdong 523808, P.R. China; ⁸Emeritus Professor, Kansai Medical University, Hirakata, Osaka 573-1010, Japan

Received March 9, 2017; Accepted June 28, 2017

DOI: 10.3892/mco.2017.1402

Abstract. Epithelioid hemangioendothelioma (EHAE) is a vascular tumor which, due to its rarity, is often misdiagnosed as other hepatic tumors based on radiological characteristics. We herein report a case of EHAE in the liver and the mesentery of the small intestine. A 64-year-old asymptomatic woman was admitted to the hospital due to a hepatic tumor identified using computed tomography (CT). An enhanced CT scan revealed multiple tumors in the liver and a tumor in the mesentery. One of the hepatic tumors and the mesenteric tumor were resected and histologically examined. The two tumors exhibited similar histological characteristics and were diagnosed as EHAE. When multiple tumors are found in the liver, EHAE should be included in the differential diagnosis, as the prognosis of EHAE differs from that of carcinoma or benign tumors.

Introduction

Epithelioid hemangioendothelioma (EHAE) is a rare low-to-intermediate-grade malignant vascular tumor derived from endothelial cells (1,2). EHAE was first described in 1975 by Dail and Liebow as an aggressive bronchoalveolar cell carcinoma (3). The term epithelioid hemangioendothelioma was introduced in 1982 by Weiss and Enzinger, who described the tumor as originating from blood vessels (1). The estimated incidence of EHAE is <1/million, with a female:male ratio

of 3:2 (4). Primary hepatic EHAE is an extremely rare occurrence and was first reported in 1984 by Ishak *et al* (5).

The aim of the present study was to report a case of EHAE presenting with multiple lesions in the liver and a lesion in the mesentery of the small intestine.

Case report

A 64-year-old woman was admitted to the Toyooka Hospital (Toyooka, Japan) in November 2013 with elevated levels of serum aspartate aminotransferase and alanine aminotransferase and due to tumors in the liver, which were identified on a computed tomography (CT) scan. The patient did not report any noticeable symptoms related to the tumor; she had diabetes mellitus and hypertension, and she was receiving treatment with estradiol dipropionate and dydrogesterone for climacteric symptoms. The patient's family cancer history was significant: Her father had been diagnosed with gastric and lung cancer, her mother had been diagnosed with pancreatic cancer, her older brother had been diagnosed with cancer of the urinary bladder, her older sister had been diagnosed with ovarian cancer, and her younger sister had been diagnosed with breast cancer.

An enhanced CT scan revealed multiple low-density tumors with an enhanced margin in the liver and a 30-mm irregular tumor in the mesentery (Fig. 1). Ethoxybenzyl-magnetic resonance imaging revealed that the tumor had high signal intensity on T2-weighted images (Fig. 2A), low signal intensity in T1-weighted images (Fig. 2B) and high signal intensity on diffusion-weighted images (Fig. 2C). These tumors also presented as hot spots on positron emission tomography/CT scan (Fig. 3). Blood tests revealed normal levels of carcinoembryonic antigen, α -fetoprotein and carbohydrate antigen 19-9. There were no abnormalities noted on the upper or lower gastrointestinal endoscopic examinations.

On laparoscopic observation, several whitish tumors were identified on the bilateral lobes of the liver and on the mesentery of the small intestine. It was impossible to resect all the tumors, since multiple lesions were present in both the left

Correspondence to: Dr Yasushi Adachi, Department of Diagnostic Pathology, Toyooka Hospital, 1094 Tobera, Toyooka, Hyogo 668-8501, Japan
E-mail: adachiya250@gmail.com

Key words: epithelioid hemangioendothelioma, liver, mesentery, female patient, hormonal therapy

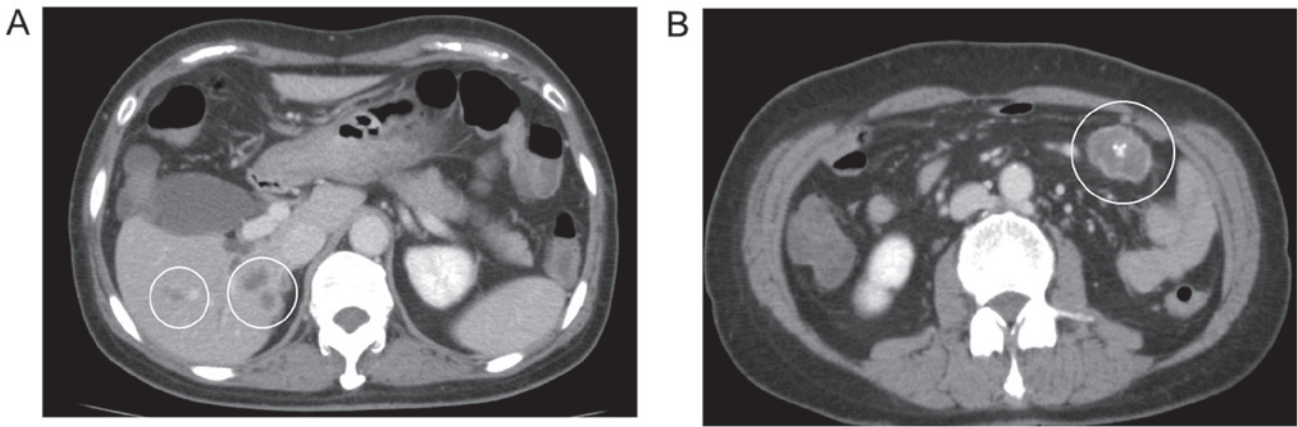


Figure 1. Enhanced computed tomography (CT) scan showing several low-density tumors with an enhanced margin in the liver and an irregular tumor in the mesentery. In the images from the enhanced CT, (A) several tumors were identified in the liver and (B) a 30-mm tumor with an irregular border was identified in the mesentery (circled areas). The tumors were low-density with an enhanced margin.

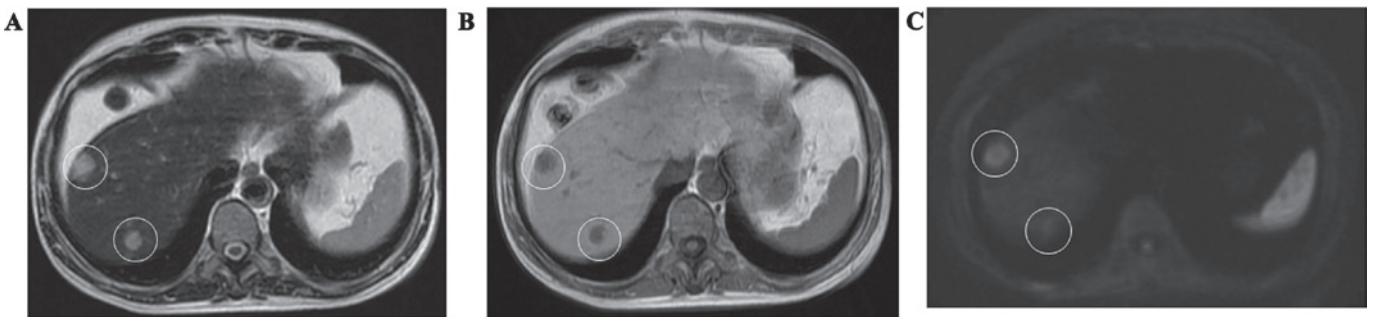


Figure 2. Ethoxybenzyl-magnetic resonance imaging examination revealed multiple intrahepatic tumors (circled areas). (A) T2-weighted image, (B) T1-weighted image and (C) diffusion-weighted image.

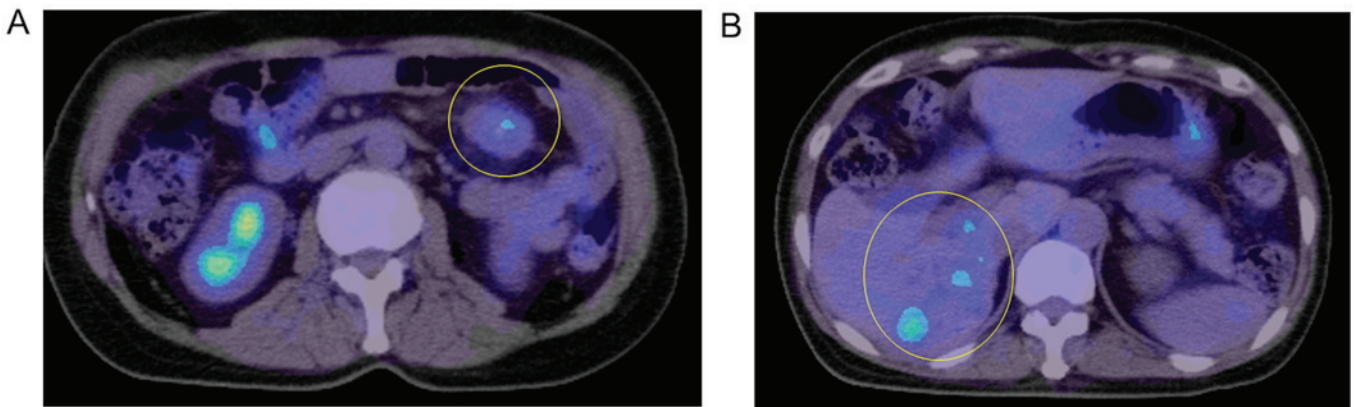


Figure 3. Positron emission tomography-computed tomography images showing (A) a hot spot in the mesentery and (B) hot spots in the liver (circled areas). Of note, in panel A, the renal pelvis appears positive, and in panel B, the contents of small intestine appear positive; these are non-specific positive reactions.

and right lobes of the liver. As we were unable to determine whether the hepatic and mesenteric tumors were of the same type by diagnostic imaging alone, resection of the mesenteric tumor and one of the hepatic tumors was attempted and the resected specimens were sent for histological examination.

The size of the mesenteric and hepatic tumors was 33x28x25 and 25x25x10 mm, respectively (Fig. 4). The tumors were hard and whitish on cross-section, and they were relatively well-defined, with irregular margins. Histologically, the two

tumors exhibited similar characteristics, such as epithelioid and dendritic cells with abundant cytoplasm and atypical nuclei (Fig. 5). In the periphery of the tumor, the tumor cells proliferated along pre-existing sinusoids. In the center of the tumor, the myxomatous stroma was conspicuous and contained tumor cells that were present either as single cells or in small groups. Some tumor cells were arranged in a trabecular pattern.

Immunohistologically, the tumor was positive for vimentin and vascular endothelial growth factor receptor (VEGFR)2,

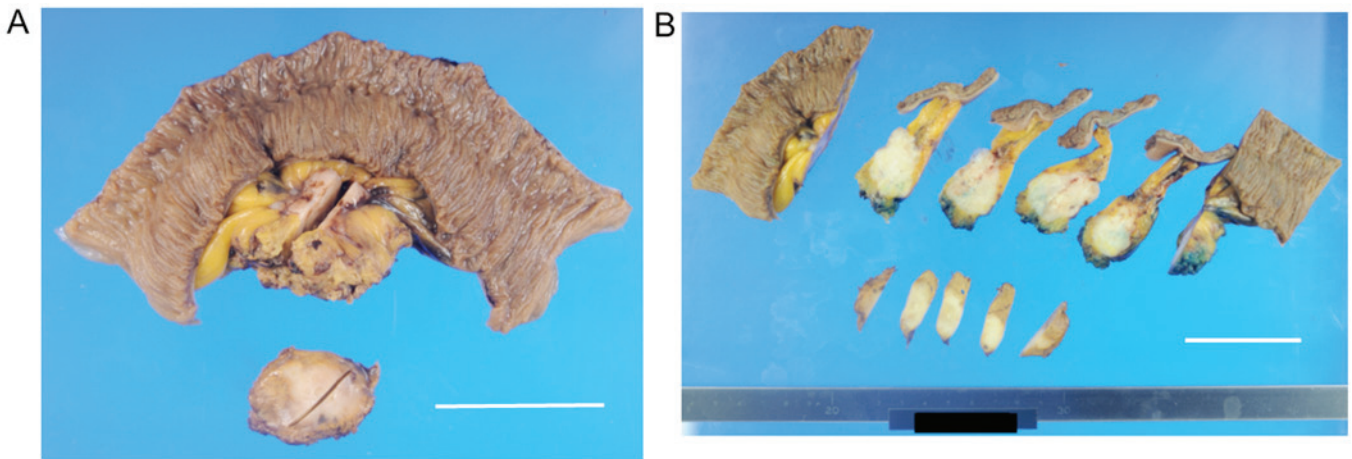


Figure 4. Macroscopic view of the formalin-fixed surgical specimens. (A) Whole images and (B) cut surfaces of the tumors are shown. The upper tumor was located in the mesentery of the resected small intestine, and the lower tumor was resected from the liver (bar, 5 cm).

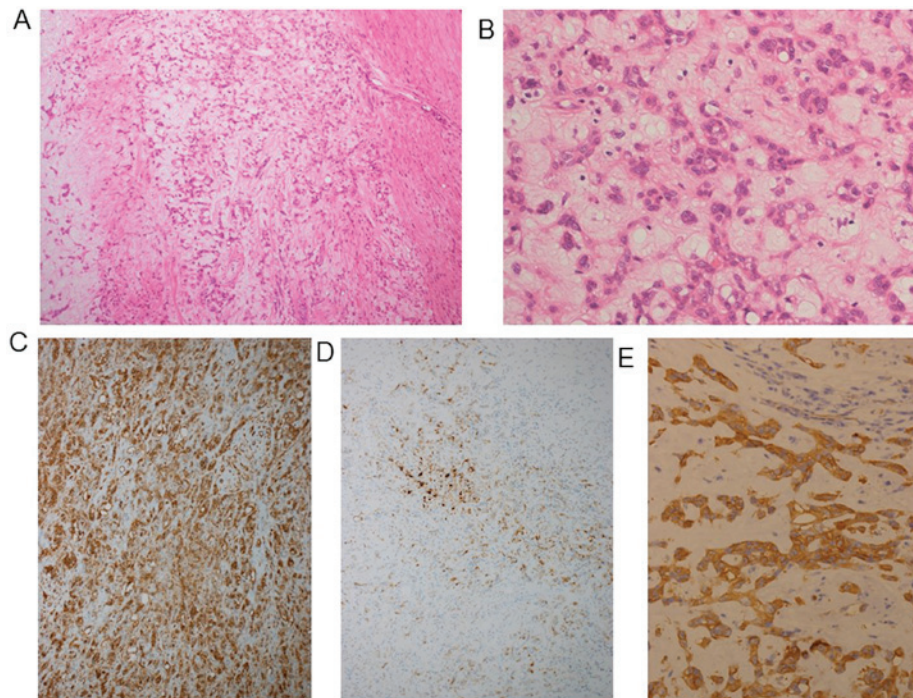


Figure 5. Microscopic findings. (A) Low-powered (magnification, x10) and (B) high-powered (objective lens, x40) microscopic images (hematoxylin and eosin staining). Microscopic images of immunohistological staining for (C) CD31 (magnification, x20), (D) CAM5.2 (magnification, x20), and (E) vascular endothelial growth factor receptor 2 (magnification, x60).

partially positive for CD31, CD34 and factor VIII, and negative for cytokeratin AE1/AE3, hepatocyte-specific antigen, c-Kit, α -smooth muscle actin and S-100, suggesting that the tumor was derived from the endothelial cells of the blood vessels (Fig. 5 and data not shown). Moreover, the tumor was partially positive for CAM5.2.

Based on the macroscopic and microscopic characteristics, as well as the results of the immunohistological examination, the tumor was diagnosed as EHAE originating in the liver with metastasis to the mesentery.

As the residual hepatic tumors were multiple and were present in both the left and right lobes of the liver, they could not all be resected. Therefore, radiofrequency ablation was performed for the hepatic lesions and the patient was treated

with pazopanib, which is a potent and selective multi-targeted receptor tyrosine kinase inhibitor that blocks tumor growth and inhibits angiogenesis, as EHAE expresses VEGFR2 (Flk-1) and platelet-derived growth factor receptor β . Approximately 3 years and 7 months after the first hospital visit, the patient maintains stable disease under pazopanib treatment (the hepatic tumors have not grown and there are no additional metastatic lesions). The patient's last follow-up was in June 2017.

Discussion

We herein described a case of EHAE arising in a 64-year-old woman presenting as multiple lesions in the liver and a single lesion in the mesentery.

It has been reported that EHAE is a rare tumor, and that its most common site of origin is the liver (4). However, some cases of EHAE originating in the mesentery or peritoneum have been reported. It is conceivable that, in the present case, the EHAE first developed in the liver and then metastasized to other sites inside the liver and to the mesentery, based on the most common EHAE site of origin and the distribution and number of the lesions.

A case of hepatic EHAE metastasizing to the mesentery was previously reported (6). In that case, there were multiple EHAE lesions in the liver and the EHAE had also metastasized to the peritoneum, omentum and mesentery, resulting in multiple organ dysfunction syndrome. In the present case, several lesions were identified in the liver but the only metastatic lesion was observed in the mesentery. The mesenteric lesion and one of the hepatic lesions were resected. As there were multiple hepatic lesions in both the left and right lobes of the liver, the resection of all the tumors was not feasible.

Epidemiologically, the estimated prevalence of EHAE is <1/million (4). EHAEs present mainly in the liver alone (21%), in the liver and the lung (18%), in the lung alone (12%), or in the bone alone (14%) (7). Mehrabi *et al* reviewed 434 cases of primary hepatic EHAE (8). The age of the patients ranged from 3 to 86 years, with a mean age of 41.7 years, and the male:female ratio was 2:3. The major symptoms of hepatic EHAE were upper abdominal pain, hepatomegaly and weight loss, although the majority of the patients were asymptomatic at the time of diagnosis. Of the hepatic EHAE patients, 87% exhibited multifocal tumors that involved the bilateralliver lobes.

The patient presented herein was female, asymptomatic, and had multifocal hepatic tumors with metastasis to the mesentery. It has been reported that extrahepatic involvement at the time of diagnosis is observed in 36.6% of hepatic EHAE patients, and that the lung (8.5%), regional lymph nodes (8.5%), peritoneum (6.1%), bone (4.9%), spleen (3.2%) and diaphragm (1.6%) are the most common sites of extrahepatic involvement (8).

In the present case, extrahepatic involvement of the mesentery was observed. These results suggest that hepatic EHAE may easily metastasize to other sites of the liver, but do not readily metastasize to other organs.

The patient was receiving estradiol dipropionate and dydrogesterone for climacteric symptoms. Factors possibly involved in the etiology of EHAE include oral contraceptives (9), vinyl chloride (10), asbestos (11), thorotrast (12), liver trauma (13), viral hepatitis (14), primary biliary cirrhosis (15) and alcohol-related hepatic disorders (6). These findings suggest that inflammation or female hormones may be associated with the development of EHAE. It has been also reported that long-term administration of female hormones, such as oral contraceptive pills, is associated with the development of liver tumors (16).

Chromosomal and genetic abnormalities have also been reported to be associated with EHAE (17-19). Errani *et al* reported that the *WWTRI-CAMTA1* fusion gene was present in EHAE, and that the same pattern of *WWTRI-CAMTA1* fusion genes occurred in each tumor of each patient with multiple EHEAs (18,19). These results suggest that the *WWTRI-CAMTA1* fusion gene may be associated with the development of EHEA, and that multiple EHAE lesions

may originate from a single lesion. Further research on the association between EHAE and genetic abnormalities, as well as other contributing factors, is required to optimize treatment.

In conclusion, we herein present a case of EHAE that presented as multiple lesions in the liver and a lesion in the mesentery, in a woman who had been receiving estradiol dipropionate and dydrogesterone for several years. Approximately 3 years and 7 months have passed since the patient's first hospital visit; she remains alive and the EHEA has not progressed. More effective therapeutic options must be developed for EHAE in the future. This case report was approved by the Ethics Committee of Toyooka Hospital and the patient consented to the publication of the case details and associated images.

Acknowledgements

The authors would like to thank Ms. H. Ogaki, Mr. K. Nagaoka, Mr. T. Kuge, Mr. H. Takenaka and Ms. S. Eriguchi of the Toyooka Hospital for their expert technical assistance. The Ethics Committee of the Toyooka Hospital and the patient approved the publication of this case report.

References

- Weiss SW and Enzinger FM: Epithelioid hemangioendothelioma: A vascular tumor often mistaken for a carcinoma. *Cancer* 50: 970-981, 1982.
- Makhlouf HR, Ishak KG and Goodman ZD: Epithelioid hemangioendothelioma of the liver: A clinicopathologic study of 137 cases *Cancer* 85: 562-582, 1999.
- Dail DH and Liebow AA: Intravascular bronchioloalveolar tumor. *Am J Pathol* 78: 6a-7a, 1975.
- Lau K, Massad M, Pollak C, Rubin C, Yeh J, Wang J, Edelman G, Yeh J, Prasad S and Weinberg G: Clinical patterns and outcome in epithelioid hemangioendothelioma with or without pulmonary involvement: Insights from an internet registry in the study of a rare cancer. *Chest* 140: 1312-1318, 2011.
- Ishak KG, Sesterhenn IA, Goodman ZD, Rabin L and Stromeyer FW: Epithelioid hemangioendothelioma of the liver: A clinicopathologic and follow-up study of 32 cases. *Hum Pathol* 15: 839-852, 1984.
- Gurung S, Fu H, Zhang WW and Gu YH: Hepatic epithelioid hemangioendothelioma metastasized to the peritoneum, omentum and mesentery: A case report. *Int J Clin Exp Pathol* 8: 5883-5889, 2015.
- Sardaro A, Bardoscia L, Petruzzelli MF and Portaluri M: Epithelioid hemangioendothelioma: An overview and update on a rare vascular tumor. *Oncol Rev* 8: 259, 2014.
- Mehrabi A, Kashfi A, Fonouni H, Schemmer P, Schmiech BM, Hallscheidt P, Schirmacher P, Weitz J, Friess H, Buchler MW and Schmidt J: Primary malignant hepatic epithelioid hemangioendothelioma: A comprehensive review of the literature with emphasis on the surgical therapy. *Cancer* 107: 2108-2121, 2006.
- Dean PJ, Haggitt RC and O'Hara CJ: Malignant epithelioid hemangioendothelioma of the liver in young women. Relationship to oral contraceptive use. *Am J Surg Pathol* 9: 695-704, 1985.
- Darras T, Moisse R and Colette JM: Epithelioid hemangioendothelioma of the liver. *J Belge Radiol* 71: 722-723, 1988.
- de Man RA, Bac DJ, van Blankenstein M and Zondervan PE: Sterile necrosis of the liver due to primary epithelioid haemangio-endothelioma presenting as fever of undetermined origin. *Neth J Med* 45: 25-29, 1994.
- Soslow RA, Yin P, Steinberg CR and Yang GC: Cytopathologic features of hepatic epithelioid hemangioendothelioma. *Diagn Cytopathol* 17: 50-53, 1997.
- Banerjee B and Rennison A: Epithelioid haemangioendothelioma of liver: A vascular tumour easily mistaken for metastatic carcinoma on ultrasound imaging. *Br J Radiol* 65: 611-613, 1992.
- Läuffer JM, Zimmermann A, Krähenbühl L, Triller J and Baer HU: Epithelioid hemangioendothelioma of the liver. A rare hepatic tumor. *Cancer* 78: 2318-2327, 1996.

15. Terada T, Hosoi M, Kono N, Watanabe K and Nakanuma Y: Epithelioid hemangioendothelioma of the liver in primary biliary cirrhosis. A case report. *Acta Pathol Jpn* 39: 607-611, 1989.
16. Kapp N and Curtis KM: Hormonal contraceptive use among women with liver tumors: A systematic review. *Contraception* 80: 387-390, 2009.
17. Boudousquie AC, Lawce HJ, Sherman R, Olson S, Magenis RE and Corless CL: Complex translocation [7;22] identified in an epithelioid hemangioendothelioma. *Cancer Genet Cytogenet* 92: 116-121, 1996.
18. Errani C, Zhang L, Sung YS, Hajdu M, Singer S, Maki RG, Healey JH and Antonescu CR: A novel WWTR1-CAMTA1 gene fusion is a consistent abnormality in epithelioid hemangioendothelioma of different anatomic sites. *Genes Chromosomes Cancer* 50: 644-653, 2011.
19. Errani C, Sung YS, Zhang L, Healey JH and Antonescu CR: Monoclonality of multifocal epithelioid hemangioendothelioma of the liver by analysis of WWTR1-CAMTA1 breakpoints. *Cancer Genet* 205: 12-17, 2012.