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Case Report

Composite hemangioendothelioma arising from the kidney: case report with review of the literature

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Abstract: Reported herein is a medical curiosities vascular tumor primary arising from the kidney and exhibiting unique histopathological features. A 32-year-old woman underwent a total nephrectomy of right kidney because of a mass localized in the inferior pole. Distinct from other vascular lesions, on histology the tumor had a peculiar composite pattern, consisting of benign and malignant vascular components, which were haphazardly intermixed without any definite margins. The malignant component was composed of epithelioid hemangioendothelioma (45%) and angiosarcoma (50%) with moderate differentiation. Immunohistochemically, the oval to cuboidal to spindle tumor cells expressed only endothelial markers (CD31, CD34 and factor VIII-related antigen). And the angiosarcomatous component was characterized by the presence of a greater proliferation index Ki-67. Unlike other epithelial tumors, smooth muscle actin (SMA), cytokeratin, EMA and S-100 were all negative in the epithelioid tumor cells. These findings led to the diagnosis of a low-grade vascular neoplasm with morphological features consistent with so-called composite hemangioendothelioma (CHE). At 11 month follow up the patient was alive, without evidence of tumor recurrence. CHE is an extremely rare vascular neoplasm, with borderline malignant potential, which mostly occurs in distal extremity of the limbs at the cutaneous level and, only 30 cases have been previously described until now. To our knowledge, this is the first report of CHE arising from the kidney and widens the spectrum of primary vascular tumors arising in the kidney.

Keywords: Composite hemangioendothelioma, hemangioendothelioma, rare tumors, kidne

Introduction

Composite hemangioendothelioma (CHE) is the most recently described vascular neoplasm of low malignant potential included in the hemangioendothelioma (HE) group [1]. CHE is an extremely rare vascular neoplasm; only 30 cases have been previously described mainly in the extremities at the cutaneous level until now [2-16]. We herein report a case of CHE affecting the right kidney of a 32-year-old female, a hitherto undescribed primary tumor site with the review of the literature hoping to understand this medical curiosities tumor better. We suggest that CHE may affect a wider range of body locations than previously reported. To our best knowledge, this is the first case of CHE arising from the kidney reported in the English literature.

Case presentation

A 32-year-old woman without family history of malignant tumor was admitted to our hospital with one-week history of an enlarging impalpable mass in the right kidney during a routine medical examination. Additional investigations were unremarkable. Laboratory results including complete blood count, routine blood chemistry, kidney and liver function tests, urine analysis, and chest radiograph were within normal limits. Enhanced computerized tomography (CT) scan of the abdomen revealed a 2.6 cm × 2.1 cm heterogeneously contrast enhancing right kidney mass occupying the lower portion of right kidney without evidence of either local invasion or lymphadenopathy (**Figure 1A**, **1B**). Subsequently performed percutaneous needle biopsy of the kidney tumor suggested a diagnosis of atypical vascular neoplasm. Because of

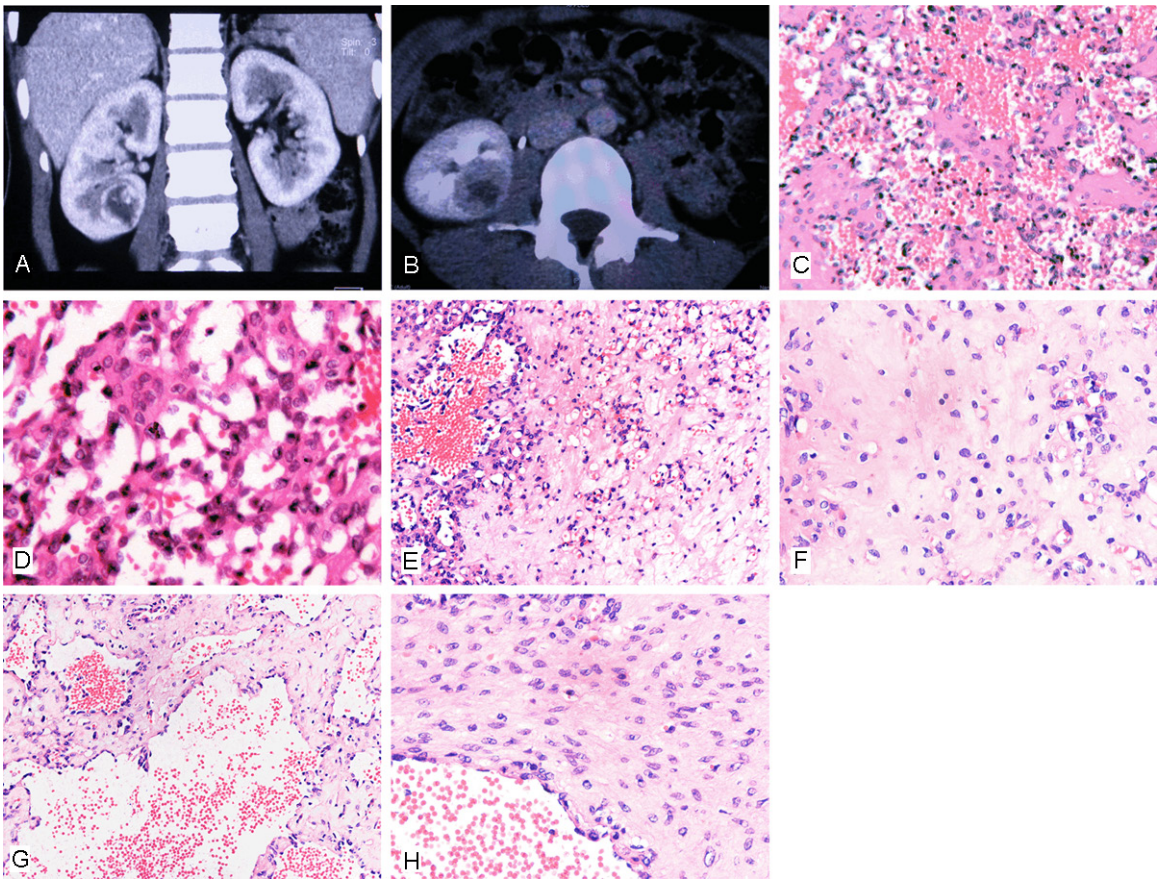

Figure 1. Contrast-enhanced computerized tomography (CT) image (A) of the abdomen revealed a 2.6 cm × 2.1 cm mass occupying the lower portion of right kidney without evidence of either local invasion or lymphadenopathy at portal venous (B) phase. Histopathologically, areas consistent with moderately differentiated angiosarcoma were characterized by vascular channels with a complex dissecting and anastomosing growth pattern (C, ×200) with the tumor cells showing marked nuclear atypia and a greater proliferation index (D, ×400). Epithelioid hemangioendothelioma-like areas showing cords, nests and trabeculae composed of epithelioid cells infiltrating the myxohyaline stroma (E, ×200). Note the occasional erythrocytes in the interior large eosinophilic cytoplasm and cytoplasmic vacuoles in the neoplastic cells (F, ×400). Areas showing irregular dilated blood vessels contain numerous red cells with a solid component associated with epithelioid spindle cells like those seen in spindle cell hemangioma (G, ×200). Detail of epithelioid growth: nests of round to slightly spindle-shaped endothelial cells embedded in densely hyalinized stroma (H, ×400).

the risk of impaired renal function, a total nephrectomy was performed.

Pathologic findings

Grossly, the resected specimen (15 cm × 9 cm × 7 cm) with attached ureter and perirenal fibroadipose tissue was received. The specimen was bisected to reveal a 1.8 cm × 1.5 cm × 0.5 cm circumscribed but unencapsulated tumor occupying the perirenal space of the lower and middle poles of kidney. The tumor was firm and showed a yellowish white to tan-gray, myxoid and lobulated cut surface with hemorrhage and necrosis. Perirenal fat was grossly not infiltrated by the tumor.

Microscopically, the histological examination showed an infiltrative vascular lesion with a complex architecture and no definite margins. Distinct from other vascular lesions, the most important feature of the tumor was the complex admixture of several histological patterns, which composed of malignant vascular components such as moderately-differentiated angiosarcomas (50%) as well as epithelioid HE (45%), and benign vascular components such as spindle cell hemangioma (5%). These areas merged imperceptibly with each other and were difficult to identify the pure components. Areas with histologic features of moderately differentiated angiosarcoma were characterized by vascular

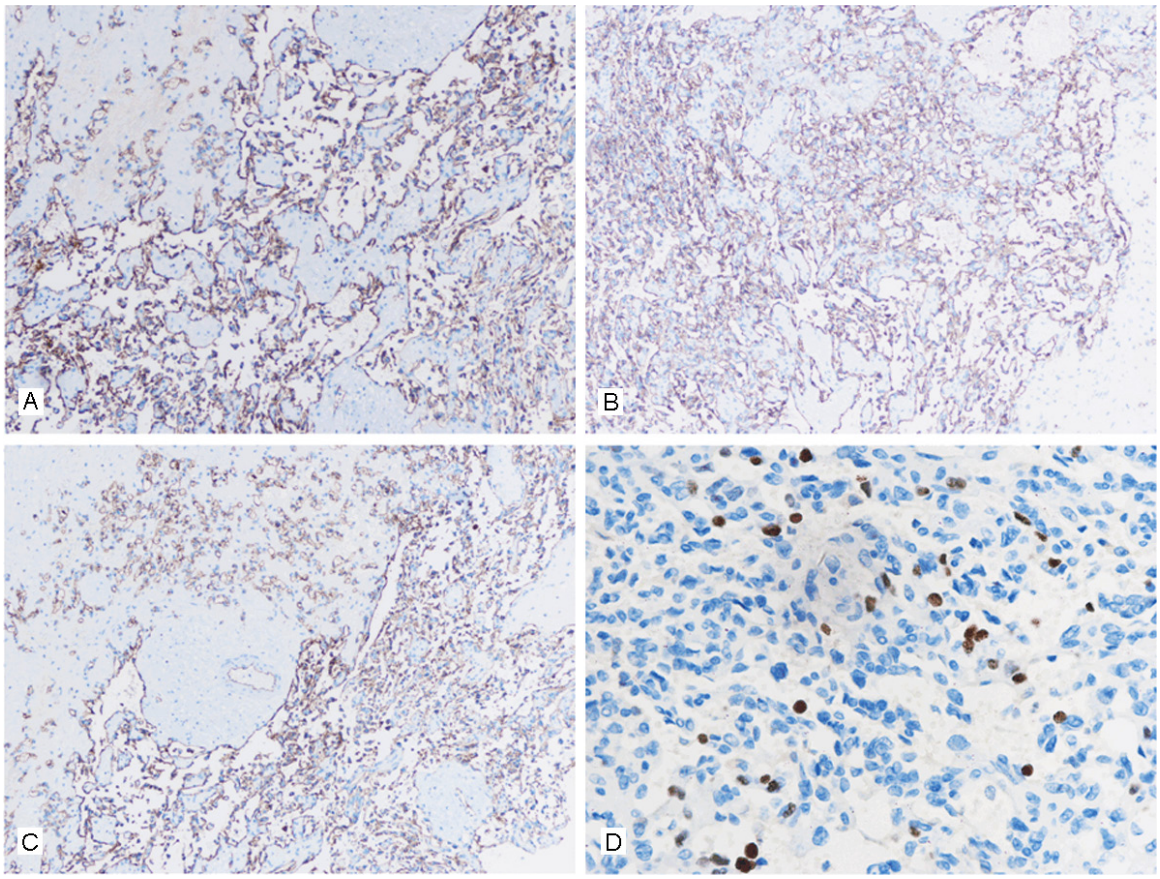

Figure 2. The immunohistochemical investigations showed a strong immunoreactivity for CD31 (A, ×100) and CD34 (B, ×100), and weak immuno-expression for factor VIII-related antigen (C, ×100) in neoplastic cells. The angiosarcomatous component was characterized by the presence of a greater proliferation index Ki-6 (D, ×400).

channels with a complex dissecting and anastomosing growth pattern associated with nuclear atypia, multilayering of atypical nuclei with vacuolated cytoplasm arranged in solid sheets, and scattered papillae without hyaline cores. Relative higher mitotic figures could be identified in this area (3 per 10 high power fields) (**Figure 1C**, **1D**). Areas with a remarkable resemblance to the histological features of epithelioid HE always composed of cords or strands of round to oval endothelial cells, with vesicular nuclei, ample eosinophilic cytoplasm with intra-cytoplasmic vacuoles, and occasional erythrocytes in the interior large eosinophilic cytoplasm, often showing vacuolization, and hyperchromatic nuclei, embedded in a myxohyaline stroma (**Figure 1E**, **1F**). Discrete areas showing histological features of spindle cell hemangioma were observed in the peripheral aspects of the neoplasm, and were composed of irregular dilated blood vessels containing numerous red cells within their lumina and spindle monomorphous cells with vacuolated cytoplasm (**Figure 1G**, **1H**). The tumor stroma of CHE was composed of fibrofatty tissue and moderate to prominent inflammatory infiltrates, predominantly of lymphocytes with occasional lymphoid follicles.

Immunohistochemically, neoplastic cells expressed strong immunoreactivity for CD31 and CD34, and weak immuno-expression for factor VIII-related antigen (**Figure 2A-C**). Unlike other epithelial tumors, smooth muscle actin (SMA), cytokeratin, EMA and S-100 were all negative in the epithelioid tumor cells. The angiosarcomatous component was characterized by the presence of a greater proliferation index Ki-67 (**Figure 2D**).

Owing to the presence of these variable histological appearances and the immunohistochemical findings, a final diagnosis of CHE was made. No adjuvant chemo- or radiotherapy was

Table 1. The main clinical features of all cases of composite hemangioendothelioma (CHE) reported to date

References	Case	Sex/Age	Site	History	Major axis, mm	Treatment	Follow up	Recurrence	Metastasis
Nayler SJ et al. [2]	1	M/42	Foot	12 years	60	Radical surgery	1 year	No	No
	2	F/27	Foot	Since childhood	20	Amputation	6 years	Yes	No
	3	M/21	Finger	Several months	N/A	Excision	13 years	No	No
	4	M/44	Finger	Several years	10	Excision	2 years	No	No
	5	M/70	Tongue	N/A	N/A	Radical surgery	11 years	Yes	Yes
	6	F/31	Foot	2 years	10	Excision	N/A	N/A	N/A
	7	F/71	Foot	6 years	40	Excision	N/A	N/A	N/A
	8	M/35	Hand	Several years	30	Excision	4 years	Yes	No
Reis-Filho JS et al. [3]	9	F/23	Forearm, hand	Since infancy	130	Amputation	7 years	No	No
Biagioli M et al. [4]	11	F/46	Toe	N/A	20	Excision	30 months	Yes	No
Fukunaga M et al. [5]	12	F/39	Ankle, foot	Since birth	300	Partial excision	39 years	N/A	No
	13	M/44	Mandibular vestibule	4-6 months	13	Excision	13 months	No	No
	14	F/75	Thigh	10 years	35	Excision	27 months	Yes	No
	15	F/37	Upper arm	Since birth	40	Excision	N/A	No	No
	16	F/22	Foot	3 years	50	Partial excision	N/A	N/A	N/A
Requena L et al. [6]	17	M/60	Leg, foot	Since childhood	N/A	Excision	several months	Yes	Yes
Fasolis M et al. [7]	19	M/38	Oral cavity	N/A	25	Excision	3 years	No	No
Utas S et al. [8]	20	F/62	Forearm, hand	4 months	90	Chemotherapy with interferon-α2b	N/A	N/A	N/A
Tejera-Vaquerizo A et al. [9]	18	F/23	Back	2 years	30	Excision	30 months	No	No
Cakir E et al. [10]	22	F/50	Mediastinum	2 months	6	Total sternotomy and resection of the mass	13 months	No	No
Aydingoz IE et al. [11]	21	F/48	Thigh	2 years	15	Total excision	4 years	Yes	Yes
Tateishi J et al. [12]	24	F/34	Nose	7 months	8	Electron beam	9 months	No	No
Yoda Y et al. [14]	23	M/67	Spleen	4 months	N/A	Splenectomy and postoperative chemotherapy	N/A	N/A	N/A
Tsai JW et al. [15]	25	F/23	Foot	5 years	40	Wide excision	7 months	No	No
	26	F/15	Hypopharynx	3 months	32	Excision	18 months	No	No
	27	F/49	Hypopharynx	2 months	24	Excision	10 months	No	No
	28	M/8	Elbow	18 months	16	Excision	48 months	No	No
McNab PM et al. [16]	29	M/66	Left lower extremity	32 years	20	Taxolmono therapy with additional chemotherapy	32 years	Yes	No
Chen YL et al. [13]	30	F/46	Neck	4 years	48	Excision	N/A	N/A	N/A
Present case	31	M/32	Kidney	1 week	18	Total nephrectomy	11 months	No	No

N/A, not available.

performed. The patient is still alive and well without evidence of local tumor regrowth and metastatic disease 11 months after the operation.

Discussion and review

In 1982, Weiss and Enzinger proposed the term HE to those vascular neoplasms showing a borderline biological behavior, intermediate between entirely benign hemangiomas and highly malignant angiosarcomas [17]. CHE is the most recently described entity of the HE spectrum. In 2000, Nayler et al. reported eight cases of a vascular neoplasm showing varying combinations of benign, low-grade malignant and malignant vascular components, and they proposed the term CHE to name this lesion and described the tumor as a low-grade malignant neoplasm [2]. To date, only 30 cases have been reported in the English literature (**Table 1**).

Clinically, patients with CHE are ranging from newborns to 75-year-old adults with a mean age of 42 and usually presents as poorly circumscribed nodules, plaques, or ulcerated tumors, with individual nodules ranging from 0.7 to 30 cm. The ratio of females to males affected is about 3:2 (18/12), which suggests a possible predilection for females. CHE is most frequently seen in the distal part of superior and inferior limbs, then in, the head and neck region as well as the trunk, almost all of which at a cutaneous level, and occasionally in mediastinum [10] and spleen [14]. The present case was a primary tumor in the right kidney, which was rare and never reported before; suggesting that CHE may affect a wider range of body locations than previously reported. CHE lesions may involve multiple parts at the same time, such as forearm/hand, thigh/foot, or leg/foot. In most cases, the lesion has been presented for several years before the diagnosis was established. Previous report also proposed an association of CHE with Maffucci syndrome which always linked to multiple enchondromas and vascular tumors or Kasabach-Merrit syndrome [5].

Distinct from other vascular lesions, CHE is histopathologically characterized by a complex admixture of different histologic components of benign and malignant vascular proliferations that varied from tumor to tumor without definite margins. There is variation in the proportions of each component as well as the manner in which each component is distributed throughout each lesion. One of the most frequent histological components observed in CHE is retiform HE, which often exhibits branching blood vessels with slender, anastomosing walls, mimicking the rete testis. These vessels haphazardly infiltrate the soft tissues and are lined by typical prominent endothelial cells with a hyperchromatic and hobnail appearance. Epithelioid HE and spindle cell hemangioma, which could be found in our case, are also the predominant components in most CHE cases. Some cases may show papillary structures similar to those of papillary intralymphatic angioendothelioma (PILA). We also reviewed some cases, in which contain areas of the benign component showed features of an arteriovenous malformation and cavernous hemangioma. Areas with Kaposiform HE features which were composed of infiltrative nodules of spindle cells, along with crescent-shaped vascular spaces could also be found in some cases. In rare instances, areas of high-grade angiosarcoma are also present, with solid aggregates of atypical pleomorphic cells and numerous mitotic figures. Moreover, these different components in CHE merged imperceptibly, making it difficult to identify the pure components.

Immunohistochemically, neoplastic cells of CHE express the usual endothelial markers, such as von Willebrand factor (vWF) and CD31, although CD34 is sometimes negative or weak positive in proliferating cells [2-6]. Immunoreactivity for SMA has been found in some stromal cells as well as in the muscular layer on non-neoplastic vessels. There was one case showing immunoreactivity for Prox-1 in the nuclei of neoplastic cells [6], supporting a lymphatic line of differentiation for this neoplasm.

CHE should be not mistaken for polymorphous HE. The latter has been described in soft tissues and lymph nodes and is histopathologically characterized by a combination of undifferentiated solid areas with evident angiomatous pattern and uniform cytologic elements, whereas CHE combines different histopathologic patterns in the same lesion.

With the exception of 3 cases treated with interferon [8] or electron beam [12], respectively, all the reported cases of CHE have been surgically excised, similar to epithelioid heman-

gioendothelioma of soft tissue [18]. However, cases in which affected areas underwent amputation seem to behave better, displaying lower recurrence rates [2, 3]. CHE has a propensity to recur locally and the ability to metastasize. Among the 30 reported cases, the neoplasm persisted locally in 8 ones and metastases developed in 3 cases 4 months to 11 years after the original surgical excision, with 2 of whom showed multiple metastases. The most common sites of metastasis were lymph nodes, followed by bones such as lumbar spine and pelvic bones, soft tissue, lung and liver [2, 6, 11]. In one case, lymph node metastases showed the histopathologic pattern of epithelioid HE [6], which seems to indicate that lesions with an epithelioid component or high-grade angiosarcoma may have a more aggressive behavior. Together with the fact that most CHE exhibited at least "angiosarcoma-like foci" and some cases had a prior history of lymphedema, which is a known risk factor for angiosarcoma, CHE may in fact be a low-grade angiosarcoma, although its prognosis is comparatively better than conventional angiosarcoma [2, 3], and should be classified as a distinct entity.

In summary, we described here a case of CHE arising in kidney for the first time. Our case is in accord with prior findings, and provides additional evidence of the coexistence of the variable components in CHE that are morphologically and biologically distinct. Both dermatologists and pathologists should be aware of the features of CHE, and this neoplasm should be considered in the differential diagnosis of vascular tumors. As suggested by various authors [6-9], surgery must be locally radical since biological behavior is still uncertain. Follow-up must be strict to make sure recurrences and metastases can be detected in time.

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Disclosure of conflict of interest

The authors declare that they have no competing interests.

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