Composite hemangioendothelioma as a rare malignant condition: a case report and comprehensive literature review

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Composite hemangioendothelioma (CHE) is a rare and little-known condition with combined benign, intermediate, and malignant features. In the current study, we describe the case of a young female with the presentations of CHE, representing the second known case in Iran. Also, we have comprehensively reviewed previous case reports of CHE. A 30-year-old female was referred with a reddish hemorrhagic painless mass in the small right finger that appeared within a few days following trauma. The mass was primarily excised but recurred within three weeks; therefore, she underwent thorough clinical, laboratory, and imaging studies. Finally, the lesions were biopsied and diagnosed as CHE. Accordingly, the involved finger was amputated, and the patient underwent chemoradiotherapy. Although CHE is a rare malignant condition worldwide, attention to the clinical presentations of this malignancy can help scientists make better therapeutic approaches leading to the best outcomes.

Keywords: hemangioendothelioma, malignancy, misdiagnosis

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INTRODUCTION

In the early 2000s, scientists reported a subtype of vascular neoplasm in eight patients with combined benign, intermediate, and malignant characteristics, identified as composite hemangioendothelioma (CHE) [1]. This neoplastic lesion invades locally, and metastasis is a rare incidence. Reddish-blue nodules in skin and soft tissue masses of the upper or lower extremities are the common presentations of CHE [2]. Rare cases of CHE have been reported in other organs such as the tongue, oral mucosa, hypopharynx, and even the spleen and kidney [3,4]. Histologically and behaviorally, CHE lies somewhere between a benign tumor (hemangioma) and a malignant lesion such as hemangiosarcoma [5]. Few cases of CHE have been reported worldwide [6]. In the following report, we discuss a young female with the presentations of CHE. This case is only the second in Iran to the

best of our knowledge. We also review previous case reports of CHE.

CASE PRESENTATION

A 30-year-old female was referred with a reddish hemorrhagic mass in the small right finger that appeared within a few days following trauma. The painless mass was only 6 millimeters in size and had a smooth surface without any roughness or ulcer. The patient's only complaint was spontaneous bleedings that ceased spontaneously as well.

The patient was referred to a surgeon, and the tumor was excised completely. Nevertheless, pinpoint lesions on the distal part of the finger appeared within three weeks. The new brown lesions were painless without any itching, irritation, burning sensations, roughness, ulceration, or even any overt alteration in the skin covering the lesions. Upon palpation, the lesions were firm and had a well-differentiated margin (Figure 1).

In the general clinical examination, there was no other similar lesion in any other part of the body. The patient only mentioned a history of hypothyroidism along with levothyroxine treatment. Besides, she had no past medical history of any hemorrhagic disorders or lesions with a similar pattern except for the excised one. Furthermore, the patient's family history was negative for any malignancy or dermatologic diseases. In the laboratory studies, the complete blood count and differentiation, coagulation tests (partial thromboplastin time, prothrombin time, and international normalized ratio), liver function tests, kidney function tests, and thyroid function tests were normal.

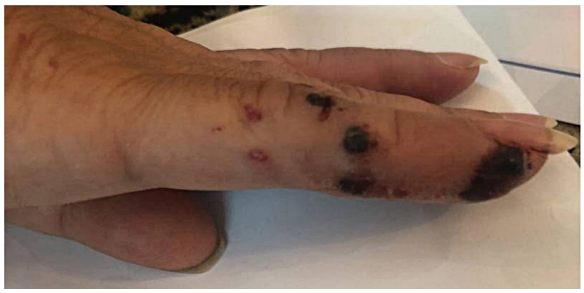

Figure 1. The lesions located on the small right finger of the patient.

Following the complete examination of the lesions, skin biopsies were taken. The biopsied lesions were firmly adherent to the underlying

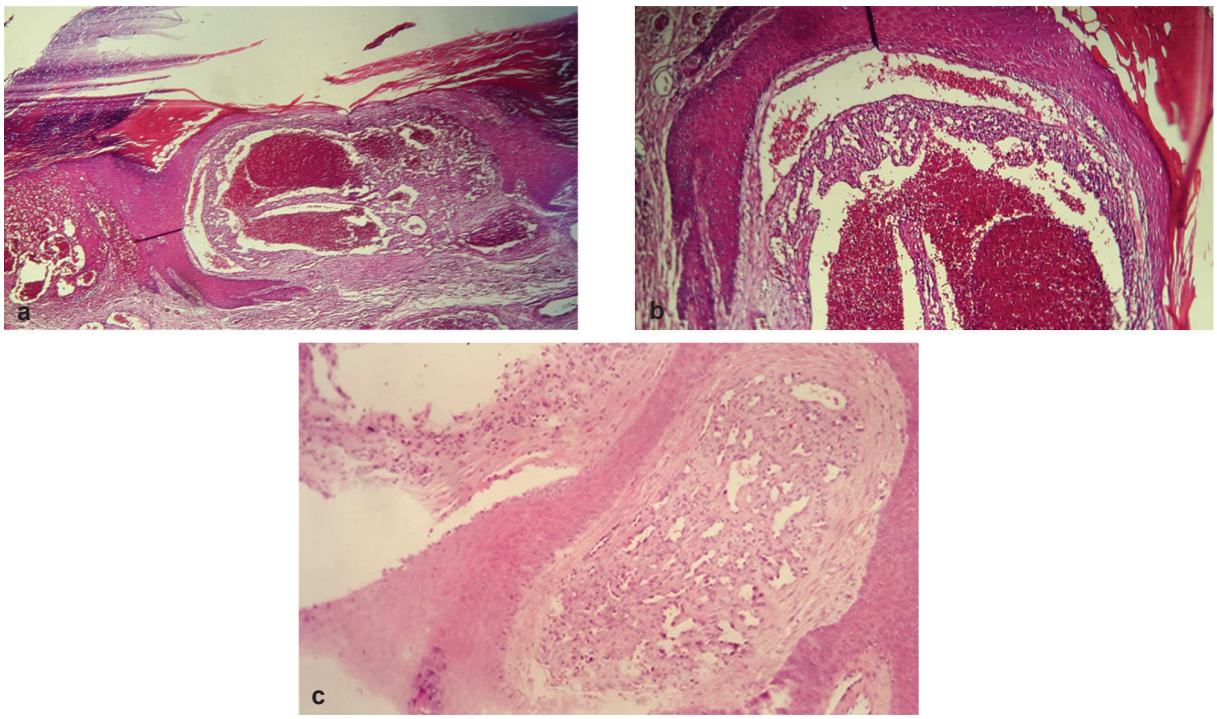

Figure 2. A & B. This section of the epidermis is acanthotic with collaret formation at the margins. Some underlying dilated blood channels are filled with erythrocytes and thrombi, surrounded by the proliferation of irregular smaller vessels lined by mildly hyperchromatic nuclei. *H&E. A: 100*×, *B: 400*×. C. In this section, the lesion resembles a pyogenic granuloma.

tissues. The mass had well-differentiated margins with an appearance in favor of vascular lesions. The biopsies were sent to the pathologist for interpretation, presenting a brown color, 6 x 5 mm lesion with a depth of 3 mm. The histologic study described the proliferation of capillary blood vessels in the dermis, some with dilated calibers in the loose fibrous stroma. Some of the endothelial cells had plump and mildly hyperchromic nuclei.

The assessed biopsies were re-interpreted by another pathologist: In the biopsied tissue, the full thickness of the dermis containing proliferated blood vessels was seen. Some of the vessels were dilated and filled with fibrin thrombi and red blood cells, and in some others, papillary formation was noted (Figure 2). In some parts, a retiform hemangioendothelioma-like pattern was also detected (Figure 3). The vessels and papillae were lined by endothelial cells, some of which were observed with hyperchromatic, hobnail nuclei, and mildly increased mitotic figures. Multinucleated endothelial cells were also noticed. The differential diagnosis proposed by the pathologists were pyogenic granuloma, amelanotic melanoma, granulation tissue, and other vascular neoplasms.

Eventually, the diagnosis of composite hemangioendothelioma (CHE) was made, and the patient was introduced to a surgeon for complete amputation of the finger. After that, she underwent chemoradiotherapy, and a positron emission tomography scan was performed. A suspicious lesion was found in the cecum part of the large intestine, which is under further evaluation.

Currently, she has been followed for six months. Fortunately, no new other lesions have been found in any part of her body. Therefore, the patient has been recommended to refer for follow-up visits every three months.

DISCUSSION

Composite hemangioendothelioma (CHE) is a condition that has rarely been reported. A summary of the reported cases is laid out in Table 1.

As can be deduced from the results of previous studies, 49 cases have been reported up to 2020. About 41% (20 cases) of the reported cases were male, while 59% (29 cases) were female. The age range for diagnosis of this disease was between 9 and 78 years. Overall, this lesion was not allocated to a specific body region and has been seen in various areas so far. Most of these lesions were observed on extremities, but rare places such as the liver, kidney, spleen, heart, pulmonary vein, nose, and oral area have also been reported. The most prevalent histopathologic appearances were epithelioid hemangioendothelioma, retiform hemangioendothelioma, spindle-cell hemangioma, and angiosarcoma-like appearance; the definitive diagnosis can be misdiagnosed with these lesions. The most common treatment was surgical excision of the CHE with a safe margin, and most of the patients did not show recurrence in the follow-up period.

The reports about CHE cases have not shown a particular range of age. Fukunaga *et al.* presented 5 cases of CHE. Among them was a 39-year-old female who had inflammation in the ankle since her birth that deteriorated by her twenties, while another was a 75-year-old female who developed a 5-cm nodule on the distal part of her right thigh from ten years beforehand [17]. However, due to the

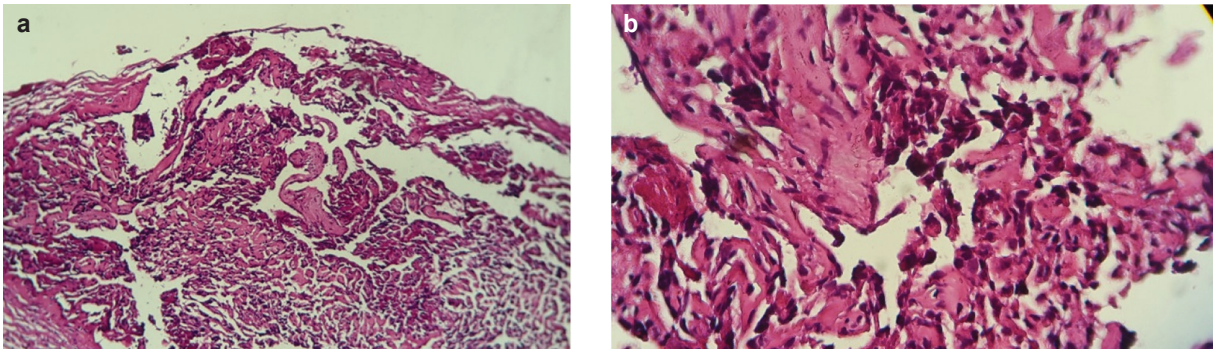

Figure 3. The vessels are irregular and somewhat resemble a retiform hemangioendothelioma-like pattern. The vessels and papillae are lined by endothelial cells, with hyperchromatic and some hobnail nuclei and a mild increase in mitotic figures. Some of the endothelial cells are multinucleated. *H&E. A: 100×, B: 400×.*

Table 1. ??????????????????????????????

Author	Case No.	Gender & age	Location	Duration	Size	Clinical features	Histopathology	Immunohistochemistry (positive markers)	Treatment	Follow-up
Mani *et al.* [7]	1	M/22	Left calcaneus	6 months	5.4 cm	Foot pain	Epithelioid HE, spindle cell H, retiform HE	ERG, CD31	Excision	Bone scan every 6 months then 1 year
	2	M/36	Ankle and foot	1 month	4 cm	Foot pain	Vascular proliferation, proliferation of infiltrative epithelioid cells	ERG, CD31	Excision	Same as case 1
Cakir *et al.* [8]	1	F/50	Middle mediastinum	2 months	6×4×2 cm	Dyspnea, cough	Retiform HE, epithelioid HE, Kaposi form HE, spindle cell H, angiosarcoma like areas	CD34, VEGF, F8-related antigen, smooth muscle actin	Total sternotomy and lesion resection	13 months, NR
Cheuk *et al.* [9]	1	F/53	Paravertebral tissue	N/A	5 cm	Back pain	Paraganglioma, spindle cell H, retiform HE, cavernous H/L, epithelioid HE	ERG, S100, CD31, synaptophysin	Excision	N/A
Chu *et al.* [10]	1	F/18	Left axilla	2 months	6×5 cm	Nodular, palpable, firm and soft lesion	AVM, capillary H, spindle cell H, cavernous H, retiform HE, epithelioid HE, kaposiform HE, angiosarcoma	CD31	Excision	2 years, alive with disease
Mahmoudizad *et al.* [3]	1	M/68	Vertex of scalp	10 months	6.3×5.3 cm	Multilobulated, violaceous, pain, pruritus	Spindle cell H, retiform HE, epithelioid HE,	CD31, factor VIII related antigen, vimentin, D2-40	Excision and radiation	Loss to follow up
Umar *et al.* [11]	1	M/9	Scalp, parietofrontal region	6 months	2×2×2 cm	Painless, mobile, dark brownish colored	Spindle cell H, Dabska's tumor, retiform HE	CD34, vimentin	Excision	18 months, NR
Nelson *et al.* [12]	1	F/38	Thoracic spine	6 months	N/A	N/A	Epithelioid, vacuolated and spindle-shaped cells with myxoid matrix	CD31, CD34, vimentin, actin	Excision	N/A

Table 1. Continued

Author	Case No.	Gender & age	Location	Duration	Size	Clinical features	Histopathology	Immunohistochemistry (positive markers)	Treatment	Follow-up
Fasolis *et al.* [13]	1	M/38	Mucosa of left cheek	6 weeks	2.5×2 cm	Enlarging, bleeding firm mass, red-grayish colored	Retiform HE, epithelioid HE, Dabska's tumor, well-differentiated angiosarcoma,	CD34, factor VIII related antigen	Excision of lesion and laterocervical LN	Every 6 months, NR
Liao *et al.* [14]	1	F/28	Chest wall	20 years and 3 months for new lesion	1×1.2 cm	Skin-colored, papules and hemorrhagic vesicles, smooth surface	Retiform HE, epithelioid HE, angiosarcoma, lymphangioma	CD31, ETS related gene	Excision	8 months, NR
Dong *et al.* [15]	1	M/56	Manubrium sterni	2 years	N/A	Sternum pain	Epithelioid HE, spindle cell H, benign H, low-grade angiosarcoma	N/A	Resection	N/A
Mao *et al.* [16]	1	M/36	Left mandible ramus	10 months	31×26 mm	No history of symptoms	Spindle cell H, retiform HE	CD31, CD34, FLI-1, D2-40	Resection and reconstruction via ilium flap	40 months, NR
Fukunaga *et al.* [17]	1	F/39	Lower thigh and foot	Since birth	30 cm	Painful, red to purple, multinodular, elastic and hard	Epithelioid HE, retiform HE, spindle cell H, angiosarcoma, lymphangioma	CD31, CD34, factor VIII related antigen	Partial excision	Alive with disease, NR
	2	M/44	Mandibular vestibule	4-6 months	1.3 cm	N/A	Epithelioid HE, retiform HE	Same as case 1	Excision	13 months, NR
	3	F/75	Lower thigh	10 years	3.5 cm	Cutaneous nodule	Epithelioid HE, retiform HE, angiosarcoma	Same as case 1	Excision	27 months, R
	4	F/37	Upper arm	Since birth	4 cm	Poorly demarcated nodule	Epithelioid HE, retiform HE, angiosarcoma, lymphangioma, AVM, angiomatosis, cavernous H	Same as case 1	Excision	Alive with disease
	5	F/22	Dorsum of foot	3 years	5 cm	N/A	Epithelioid HE, retiform HE	N/A	Excision	N/A
Yoda *et al.* [18]	1	F/67	Spleen	4 months	N/A	Large cystic lesion within solid masses	Spindle cell H, cavernous H, retiform HE	CD31, FLI-1	Splenectomy	N/A

Table 1. Continued

Author	Case No.	Gender & age	Location	Duration	Size	Clinical features	Histopathology	Immunohistochemistry (positive markers)	Treatment	Follow-up
Zhang *et al.* [4]	1	F/32	Kidney	1 week	1.8×1.5×0.5 cm	Firm impalpable mass	Moderately-differentiated angiosarcoma, epithelioid HE, spindle cell H	CD31, CD34, factor VIII related antigen	Total nephrectomy	11 months, NR
Chin *et al.* [19]	1	F/67	Skeletal muscle of forearm	3 years	3×2.7 cm	Enlarging, painful mass	AVM, spindle cell H, retiform HE, Well-differentiated angiosarcoma	CD31, CD34	Only excisional biopsy	4 months, NR
Chen *et al.* [20]	1	F/46	Neck	4 years	4.8×3.7×2.1 cm	Firm and oval mass, greyish-red colored	Epithelioid HE, retiform HE, angioendothelioma	CD31, CD34	Excision with 1 cm safe margin	N/A
BHAT *et al.* [21]	1	M/31	Upper back	1 year	1.7×1.6 cm	Violaceous nodule, firm, mobile, painless, superficial ulcerations	Epithelioid HE, retiform HE, angiomatous areas	CD34	Wide excision	5 months, NR
Leen *et al.* [22]	1	M/43	Submandibular area	3 months	2.2 cm	Firm mass	Spindle cell H, epithelioid HE, retiform HE, angiosarcoma	CD31, ERG, D2-40, CD34	Excision with neck dissection	8 months, NR
Liau *et al.* [23]	1	F/24	Temproparietal scalp	Several months	1.5 mm	Alopecia, painful firm mass	Epithelioid HE, retiform HE, Dabska's tumor, low-grade angiosarcoma	CD31, FLI-1	Excision with 2-3 cm safe margin and skin graft	1 year, NR
Stojsic *et al.* [24]	1	M/58	Gluteal region	Several years	58×31×22 mm	Slowly enlarging nodule, bluish-purple color	Retiform HE, sinusoidal H, arteriovenous H, angiosarcoma	CD31, CD34, factor VIII related antigen	Surgical excision	3 months, NR
McNab *et al.* [25]	1	M/75	Previous surgical site in lower knee and inguinal area	9 years	0.6×0.4 cm	Painful scar tissue with induration, bluish with flesh-colored nodules	Kaposi-sarcoma, adipocyte-like cells and mucinous areas	CD31, CD34, CK8/18, AE1/AE3	Taxol monotherapy every 3 weeks up to 3 cycles	Additional chemotherapy after 3 months due to increased pain

Table 1. Continued

Author	Case No.	Gender & age	Location	Duration	Size	Clinical features	Histopathology	Immunohistochemistry (positive markers)	Treatment	Follow-up
Perry *et al.* [26]	1	M/47	Wrist	N/A	7.7 cm	N/A	N/A	CD31, ERG, FLI-1, Synaptophysin, CD56	N/A	Overall 6-28 months
	2	F/48	Ankle	N/A	N/A	N/A	N/A	CD31, ERG, FLI-1, Synaptophysin, CD34	N/A	
	3	F/36	Periaortic	N/A	2.1 cm	N/A	Neuroendocrine-appearing and myoid-appearing cells	CD31, ERG, FLI-1, Synaptophysin, D2-40, CD56	N/A	
	4	F/48	Vertebral	N/A	N/A	N/A	Nested and retiform HE, H like vascular channels	CD31, ERG, FLI-1, Synaptophysin, D2-40	N/A	
	5	M/27	Pulmonary vein	N/A	N/A	N/A	N/A	CD31, ERG, FLI-1, Synaptophysin, CGA, CD56	N/A	
	6	F/14	Ear	N/A	3 cm	N/A	N/A	CD31, ERG, FLI-1, Synaptophysin, CD34, CD56, D2-40	N/A	
	7	F/55	Superficial hip	N/A	0.4 cm	N/A	N/A	CD31, ERG, FLI-1, Synaptophysin, D2-40	N/A	
	8	M/55	Liver	N/A	6.9 cm	N/A	N/A	Synaptophysin	N/A	
	9	M/15	Foot	N/A	1.2 cm	N/A	N/A	CD31, FLI-1, Synaptophysin, D2-40, CD34	N/A	
	10	F/59	Cheek	N/A	9.5 cm	N/A	Retiform dilated vascular channels, H-like and epithelioid regions	CD31, ERG, FLI-1, Synaptophysin, D2-40, CD34, CD56, D2-40	N/A	
	11	M/9	Index finger	N/A	N/A	N/A	Retiform areas with highly infiltrating areas	CD31, ERG, FLI-1, Synaptophysin, D2-40, CD34, D2-40	Amputation of finger	
Gok *et al.* [27]	1	M/54	Paraspinal muscle	2 year	3×2.5×2 cm	Back pain	Spindle cell H, epithelioid HE, retiform HE, Kaposi sarcoma	CD31, CD34, factor VIII related antigen, Podoplanin	Excision	N/A
Filho *et al.* [28]	1	F/23	Forearm and hand	Since first month of birth	13×13×7 cm	Tender mass with ulceration, reddish-brown colored	Spindle cell H, epithelioid HE, retiform HE, angiosarcoma, cavernous H	CD31, CD34, factor VIII related antigen	Below elbow amputation	7 years, NR

Table 1. Continued

Author	Case No.	Gender & age	Location	Duration	Size	Clinical features	Histopathology	Immunohistochemistry (positive markers)	Treatment	Follow-up
Requena *et al.* [29]	1	M/60	Leg, foot and inguinal fold	Since childhood	N/A	Firm erythematous nodules	Epithelioid HE, retiform HE, epithelioid HE in metastatic LNs	CD31, CD34, factor VIII related antigen, MIB-1, Prox-1 antibody	First excision, then recurrence after months, finally chemotherapy with lymphadenectomy	N/A
Rokni *et al.* [30]	1	F/78	Left forehead and right upper eyelid	18 months	5×3×1 cm	Slowly growing, painless proptosis	Proliferative solid epithelial cells, retiform structure	CD31, CD34	Partial excision with skin graft and chemotherapy	N/A
Vaquerizo *et al.* [31]	1	F/32	Upper central region of back	2 years	3 cm	Multilobulated and ulcerated mass, brownish-purple colored	Epithelioid, lipoblastic, hobnail appearance, spindle cell H, angiosarcoma	CD31	Excision with 2 cm safe margin	30 months, NR
Tsai *et al.* [32]	1	F/23	Foot	Recently	40 mm	With neurofibromatosis type 2	Epithelioid HE, retiform HE	CD31, CD34, FLI-1, D2-40	Excision	7 months, NSR
	2	F/15	Hypopharynx	3 months	55×42×32 mm	Bloody saliva, lumpy sensation in throat	Spindle-cell H, angiosarcoma	CD31, CD34, FLI-1	Excision	18 months, NSR
	3	F/49	Hypopharynx	N/A	24×22×15 mm	Hoarseness, dyspnea, mild dysphagia	Epithelioid HE, retiform HE	CD31, CD34, FLI-1, D2-40	Excision	10 months, NSR
	4	M/9	Elbow	18 months	16 mm	Mobile nodule without ulceration	Spindle-cell H, retiform HE	CD31, CD34, FLI-1, D2-40	Excision	48 months, NSR
Tateishi *et al.* [33]	1	F/34	Nose	7 months	8×8 mm	Tender nodule, dark red colored	Epithelioid HE, retiform HE	CD31, CD34, factor VIII related antigen, D2-40, VEGF	Electron beam	9 months
Utas *et al.* [34]	1	F/62	Forearm and hand	4 months	5×9 cm	Tender mass, purple colored	Epithelioid HE, retiform HE, Spindle-cell H, cavernous H, angiosarcoma	CD31, CD34, factor VIII related antigen	Interferon alpha 2b treatment	N/A
Langguth *et al.* [35]	1	F/50	Pericardium of atrioventricular junction	N/A	9.2×5.9×5.8 cm	Right atrium compression, atrial fibrillation	Epithelioid HE	N/A	Surgical resection	N/A

AVM: arteriovenous malformation, HE: hemangioendothelioma, H: hemangioma, LN: lymph node, NR: no recurrence, R: recurrence, N/A: not available

limited number of cases with CHE, the gender distribution cannot be well-established, although most of the reported cases were female [22].

The etiology of CHE is undefined as there are patients who have been born with this condition [17]. This is while McNab *et al.* introduced a 75-year-old patient with a history of melanoma with myxoid liposarcoma who underwent surgical treatment and radiation therapy. Their patient had a long-term history of lymphedema and had a small mass for more than 20 years at the site of previous surgery. The lesion was primarily diagnosed as dermatofibroma but recurred within nine years as a red bluish indurate mass at the site of previous surgery; eventually, the diagnosis of CHE was made [25].

The site of involvement in CHE is another critical point. Despite the diversity in the presented studies, approximately half of the cases had lesions on the skin of the extremities, fingers, and toes. Still, the involvement of internal organs has also been reported. For instance, one of the cases in the study of Zhang *et al.* was a 32-year-old female who underwent a right kidney nephrectomy due to a lesion located at the inferior pole of the kidney. The excised tumor was then biopsied, and the histological study revealed a vascular composite of combined malignant and benign tissues with poorly differentiated margins. She was eventually diagnosed with CHE [4].

Metastasis is a significant issue also affecting the treatment approach of CHE. Although recurrence at the primary site of the tumor has been noticed in one-third of cases, distant metastasis is a rare incident [36,37]. The only metastatic tumor was an 18-year-old female with a palpable auxiliary tumor. The pathologic study of the excised tumor was a combination of benign and malignant tissues in which the malignant sites were similar to hemangiosarcoma and kaposiform hemangioendothelioma. The patient was referred with numerous distant bone metastases within four months, with pulmonary and liver metastases occurring subsequently [37].

The current presented case in our study is the second one in Iran and the Middle East. The first case was a 78-year-old female in Tabriz, northwest of Iran, presenting with painless inflammatory lesions on the left forehead and right upper eyelid. Further evaluations revealed cervical lymph node involvement. Therefore, thorough clinical and radiological studies were performed, and the lesions and involved lymph nodes were excised. The diagnosis of CHE was made, and chemotherapy was initiated [38].

The etiology of CHE is unclear; nevertheless, our patient described a recent history of trauma. Trauma is among the precursors that can activate the cascade of inflammation in the body, even systemic inflammation. On the other hand, trauma can lead to the formation of vascular lesions; besides, immune system activation due to trauma causes hyperemia at the site of injury that may lead to local microvascular system injury as well [14,22]. It seems logical to seek either trauma or other conditions posing inflammation in the local vascular system among the new cases diagnosed as CHE.

Another remarkable point about this case was the early recurrence within a short time of three weeks following the tumor resection. Although recurrence is usual in CHE, most of the cases have presented intervals of months to years. Therefore, the recurrence in the current case may have happened due to incomplete lesion dissection and remnants of the primary etiology at the site of the lesion. Besides, hypothyroidism may have occurred following thyroiditis, which is an autoimmune reaction. Indeed, traces of autoimmunity may be found in further evaluations of CHE within a few years.

The most significant issue in this patient was the presence of an intestinal lesion in the PET scan that should be assessed thoroughly. We do not know the exact association of the intestinal lesion with CHE, but if the malignancy is concerned, the risk of metastasis should not be underestimated, which is a remarkable point for deciding on the therapeutic approach. Besides, in addition to local development, CHE may lead to neoplasia in other body sites with similar autoimmune mechanisms. Unfortunately, we have not assessed tumor markers and immunologic indices in the presented case.

CONCLUSION

Although CHE is a rare malignancy and has affected a few people worldwide, attention to the clinical presentations of this malignancy can help clinicians make better therapeutical approaches, leading to the best outcomes.

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