

Primary Cardiac Kaposiform Hemangioendothelioma: The Rare Adult-Onset. Review of the Literature

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Abstract

Hemangioendothelioma (HE) is the term used to name vascular neoplasms that show a borderline biological behaviour, intermediate between entirely benign hemangiomas and highly malignant angiosarcomas. The HE are classified in several types (papillary intralymphatic, kaposiform, epithelioid, retiform, pseudomyogenic and composite). Each of them have characteristic histo-pathological features and in the most of cases they present in childhood. The current scientific literature about HE is limited: infant and child case reports but lack of adult cases. In particular no reported primary cardiac kaposiform HE has been described in the adult within nowadays. We analyzed all scientific literature and reported an outstanding and extremely rare case of primary cardiac kaposiform HE in the adult and make a comprehensive analysis of the scientific literature of this unusual interesting but not enough known issue.

Keywords: Hemangioendothelioma; Kaposiform; Cardiac Tumor; Tumor of the Heart; Kasabach-Merritt

Introduction

Hemangioendothelioma (HE) describes vascular neoplasms with a borderline biological behaviour, intermediate between hemangiomas and malignant angiosarcomas [1]. Kaposiform hemangioendothelioma (KHE) is composed of several solid poorly circumscribed nodules with a mixture of small capillaries and solid lobules of endothelial cells arranging in a glomeruloid pattern. KHE is a rare congenital vascular tumor arising from vascular endothelial cell lining and 60% of it occurred in neonates. Kasabach-Merritt phenomenon (KMP) included thrombocytopenia, microangiopathic hemolytic anemia and mild consumptive coagulopathy, and developed often in KHE, Kaposiform lymphatic anomaly (KLA) and tufted angioma (TA). KHE with KMP had a high mortality rate of up to 50% [1-3].

Review Details

A research in MEDLINE/Pubmed and Web of Science was performed to identify the relevant case reports and case series in English using the following terms: Hemangioendothelioma, Kaposiform Hemangioendothelioma, Cardiac Hemangioendothelioma and Kasabach-Merritt syndrome or Kasabach-Merritt phenomenon. All the case reports were screened under the following criteria: 1) adult patient; 2) HE confirmed histopathologically by surgical removal or biopsy during hospitalization; 3) HE confirmed histopathologically by autopsy

during hospitalization; or 4) HE confirmed histopathologically by autopsy in sudden death. We identified a total of 235 articles published between 1952 and 2017, with 34 cases of kaposiform hemangioendothelioma (Table 1) and 24 cases of cardiac hemangioendothelioma not kaposiform (Table 2) meeting the previous criteria. Finally we confirmed and reported the first case of primary cardiac kaposiform hemangioendothelioma in the adult.

Author	Year	Pts	Age	Gender	Site	Other details
Bhutto, <i>et al.</i> [45]	1995	9	75 - 93	Male -female	Cutaneous	Irradiation, IL-2 injection, and/or surgery
Metzel, <i>et al.</i> [46]	1998	3	48 - 64	Male -female	Chest wall, neck, groin and buttock	CD 34/CD 31 positive
Zamecnik, <i>et al.</i> [47]	2000	1	39	Male	Cutaneous	Diffuse immunoreactivity of CD 99
Mac Moune Lai, <i>et al.</i> [48]	2001	1	39	Female	Right arm	Infection and bone fracture
Mac Moue Lai, <i>et al.</i> [49]	2001	1	23	Female	Left thigh	Treated with interferon alpha-2B and surgery
Cooper, <i>et al.</i> [50]	2002	1	26	Female	Left thigh	/
Hardisson, <i>et al.</i> [51]	2002	1	27	Male	External auditory canal	Radiation therapy with benefits
Chu, <i>et al.</i> [52]	2003	1	41	Female	Left side of neck	HVB and HCV positive
Beinamé, <i>et al.</i> [53]	2006	1	72	Male	Right shoulder	Giant tumor (50 cm)
Senturk, <i>et al.</i> [79]	2006	1	/	Male	/	/
Vetter-Kauczok, <i>et al.</i> [54]	2008	1	36	Female	Chest	/
Karnes, <i>et al.</i> [55]	2009	1	49	Male	Left upper arm	Treated with interferon alpha-2B
White, <i>et al.</i> [56]	2009	1	ND	Male	Tongue	/
Yu, <i>et al.</i> [57]	2010	1	36	Female	Spleen	CD34, CD31, and vimentin
Kim, <i>et al.</i> [58]	2011	1	51	Female	Breast	Performed mastectomy
Costa, <i>et al.</i> [59]	2013	2	< 60	Male	Intratesticular	/
Wu, <i>et al.</i> [60]	2013	1	ND	ND	Chest wall	Excision and CW reconstruction
Wong, <i>et al.</i> [61]	2014	1	46	Female	Paranasal sinus	Excision en bloc
Wang, <i>et al.</i> [62]	2014	1	51	Male	Ileum	Treated by Cyberknife
Zang, <i>et al.</i> [63]	2015	1	41	Female	Nasal cavity	3D/CT finding
Dong, <i>et al.</i> [64]	2016	1	22	Female	Mesentery and ileum	PET/CT finding
Elkoundi, <i>et al.</i> [80]	2016	1	87	Female	Right leg	Transfemoral amputation
Vashi, <i>et al.</i>	2016	1	38	Male	Tongue	Surgical excision
Cottini, <i>et al.</i> (presentedCase)	2017	1	30	Female	Cardiac	vv-ECMO

Table 1: Cases of kaposiform hemangioendothelioma in the adult reported in scientific literature from 1995 to 2016. ND: Non-Defined; v-v ECMO: Veno-Venous Extracorporeal Membrane Oxygenation; 3D-CT: Three-Dimensional Computed Tomography; PET/CT: Positron Emission Tomography/Computed Tomography; CW: Chest Wall; HVB: Hepatitis B Virus; HVC: Hepatitis C Virus; CD: Cluster of Differentiation.

	Reference	Year	Age	Sex	Localization	HE Type	Presentation
1	Blanchard., <i>et al.</i> [26]	1952	29	M	R Auricle	ND	Chest pain
2	Crenshaw., <i>et al.</i> [27]	1959	36	F	RA	ND	Chest pain
3	Allaire., <i>et al.</i> [5]	1964	/	/	/	ND	/
4	Hayward., <i>et al.</i> [6]	1979	49	F	MV	Epitheloid	Diastolic murmur typical of mitral stenosis
5	Singal., <i>et al.</i> [7]	1987	19	F	LA	Epitheloid	Heart murmur, clubbed finger
6	Di Biasi., <i>et al.</i> [8]	1988			RV	Epitheloid	/
7	Gegenbach., <i>et al.</i> [9]	1991	/	/	LV	Epitheloid	Incidentally discovered on echocardiogram
8	Montes Orbes., <i>et al.</i> [13]	1991	56	F	PV	Epitheloid	Thromboembolism
9	Marchiano., <i>et al.</i> [10]	1993	71	F	RA	Epitheloid	Palpitation, dizziness, low grade fever
10	Bille., <i>et al.</i> [11]	1993	59	M	AV	Epitheloid	Stroke
11	Di Biasi., <i>et al.</i> [12]	1995	35	M	RV	ND	Dyspnoea
12	Agaimy., <i>et al.</i> [13]	2002	68	M	RV/TV	Epitheloid	Incidentally discovered antopsy
13	Kitamura ., <i>et al.</i> [14]	2005	36	F	RA	Epitheloid	Cardiac tamponade
14	Vall Bernle ., <i>et al.</i> [15]	2005	69	F	MV	Epitheloid	Edema, exertional dyspnea
15	Wang ., <i>et al.</i> [16]	2006	36	F	RA	/	Dyspnoea
16	Moulai., <i>et al.</i> [17]	2006	53	M	CS	Epitheloid	Incidentally discovered on echocardiogram
17	Lisy., <i>et al.</i> [18]	2006	61	M	LA	Epitheloid	Incidentally discovered on echocardiogram
18	Safirstein., <i>et al.</i> [19]	2007	51	F	RA	Epitheloid	Incidentally discovered on echocardiogram
19	Messias ., <i>et al.</i> [20]	2008	21	F	LA	Epitheloid	Chest pain
20	Kahlout M., <i>et al.</i> [21]	2009	44	F	RA	Epitheloid	Cardiac tamponade
21	Lahon., <i>et al.</i> [22]	2012	29	F	SVC	Epitheloid	widened superior mediastinum noticed on a routine chest radiograph
22	Sugimoto T [23]	2013	77	F	RA	Epitheloid	Incidentally discovered on echocardiogram
23	Allain., <i>et al.</i> [24]	2014	/	/	SVC/RA	Epitheloid	/
24	Ellouze., <i>et al.</i> [25]	2015	53	M	RA	Epitheloid	Incidentally discovered on echocardiogram
25	Cottini., <i>et al.</i> (present case)	2017	36	F	RA	Kaposiform	Alveolar Hemorrhage

Table 2: Cases of Cardiac hemangioendothelioma in the adult reported the scientific literature. All of them were epitheloid types. M: Male; F: Female; ND: Non-Defined; R auricle: Right Auricle; RA: Right Atrium; MV: Mitral Valve; LA: Left Atrium; RV: Right Ventricle; LV: Left Ventricle; PV: Pulmonary Valve; AV: Aortic Valve; TV: Tricuspid Valve; CS: Coronaric Sinus; SCV: Superior Vena Cava.

Our Experience

A 23-year-old female with unremarkable medical history was recovered to Our Thoracic Intensive Care Unit for fever, cough evolving in acute respiratory failure with onset severe hemoptysis. The patient underwent immediately non-invasive ventilation cycles (NIVCs).

As the consequence of worsening respiratory failure and severe bleeding of the airways, the patient was referred to cardiovascular intensive care unit, intubated and started mechanical ventilation with high positive-end-expiratory-pressure (PEEP 12 cm H₂O), elevated fraction of inspired oxygen (FiO₂ 1). She started pharmacological therapy with steroids (methylprednisolone, loading dose of 1 mg/kg and then 1 mg/kg/die) and antibiotic prophylaxis in the suspect of pneumonia.

Several viral and bacterial tests were collected including Herpes virus 6-7-8, and many specific laboratory tests, such as C3-C4, anti-neutrophil cytoplasmic-antibody (ANCA), anti-nuclear antibodies (ANAs), anti-extractable nuclear antigen (ENA), lupus anticoagulant, anti-cardiolipin-antibodies, anti-B2 glycoprotein-antibodies, in order to detect vasculitis or autoimmune diseases. All microbiological and immune tests resulted negative.

A Computed Tomography (CT) of the chest revealed wide bilateral infiltrates with the preservation of small apical areas (Figure 1a, b).

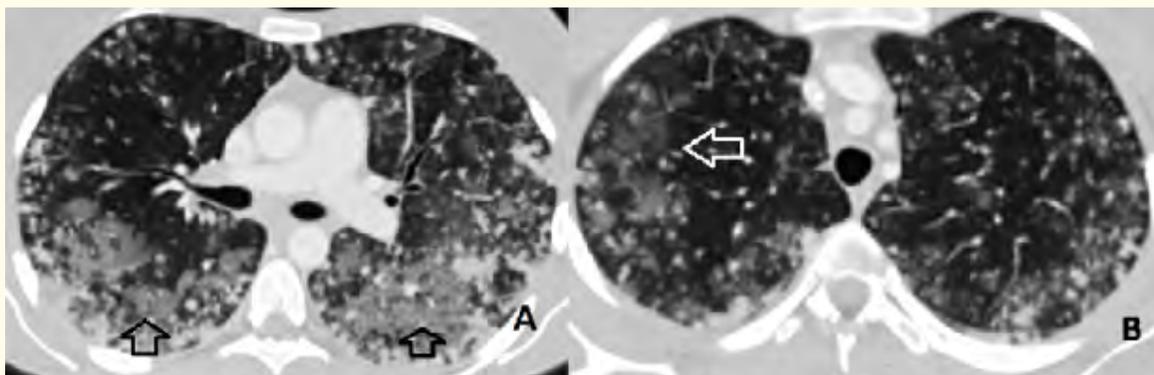


Figure 1: CT axial scan showed areas of dense consolidation (a, black arrows), patchy areas of “ground glass” opacification (b, white arrow).

Otherwise the respiratory and pharmacological supports, the hemodynamic assessment got worse: lab works revealed White Blood Cell (WBC) count of 14.250 cells/ μ l, Hemoglobin (Hb) 10.2 gr/dl, Platelet count (PLT) 148.000 cells/ μ l, the Murray score was 3.5 and arterial blood gas (ABG) was pH 7.27, PaO₂ 61.1 mmHg, PaCO₂ 67 mmHg. FiO₂ 1, clinical exam documented general swelling, no cutaneous abnormalities, no adenopathies, low bilateral pulmonary murmur and no heart murmur.

The patient underwent to implantation of veno-venous ExtraCorporeal Membrane Oxygenation (ECMO, Figure 2): a 17 Fr Biomedicus (Medtronic Minneapolis MN) cannula was inserted into the right internal jugular vein (RiJV) using Seldinger technique, 21 Fr Biomedicus (Medtronic Minneapolis MN) cannulae was surgically placed into the right femoral vein (RFV) and the correct position of both cannulae was verified through transesophageal echocardiogram (TEE). ECMO support (Pump Maquet®, Rotaflow System Console, Oxygenator Maquet®ELS System) was started with blood flow at 70 ml·Kg⁻¹·min⁻¹ and gas flow at FiO₂ 0.9 and Air 2 l/min. Protective ventilation was adopted with the following settings: Synchronized-Intermittent-Mandatory-Ventilation (SIMV), respiratory rate 10 b/min, PEEP 8 cm H₂O, PSV 16 cm H₂O, Tidal volume 6 ml/kg, FiO₂0.6. At the same time, continuous heparin infusion was administered to maintain activated partial thromboplastin time (aPTT) between 50 - 60 seconds. The ECMO performance was good but considering the continuous airway bleeding, the persistent decreasing of PLT count (less than 80.000 cells/ μ l), we have tested for Heparin-Induced-Thrombocytopenia (HIT) after 4th post-ECMO implantation day: it resulted positive. In that moment, according to the clinical patient status and coagulative disorder, we had high suspicion of Kasabach-Merritt phenom. Transfusions of platelets, fresh frozen plasma, fibrinogen concentrate (Haemocompletan®), rFVII (Novoseven®Norvodisk), and DDVAP (Emosint®TM) were administrated to stop or reduce airway bleeding. Multiple bronchoscopic examinations showed a severe diffuse alveolar hemorrhage, requiring the instillations of adrenalin (1:100.000) and tranexamic acid without beneficial effects. On the 6th post-ECMO implantation day, a more accurate TEE evidenced an unusual thickening in the right atrial wall, firstly interpreting as thrombotic apposition but the autopsy revealed this was a primary cardiac KHE arising from the entire

thickness of the right atrial wall and involving right and left pulmonary veins, infiltrating both lungs and myocardium. The immunohistochemical examination documented positive CD 31 and CD 34 (Figure 4), the specialist preparation highlighted the irregular nodules of malignant cells characterized by proliferation of spindle cells, and numerous corpuscles and micro-thrombi presented in tumor cells and endothelium with hyaline globules (Figure 4-5).

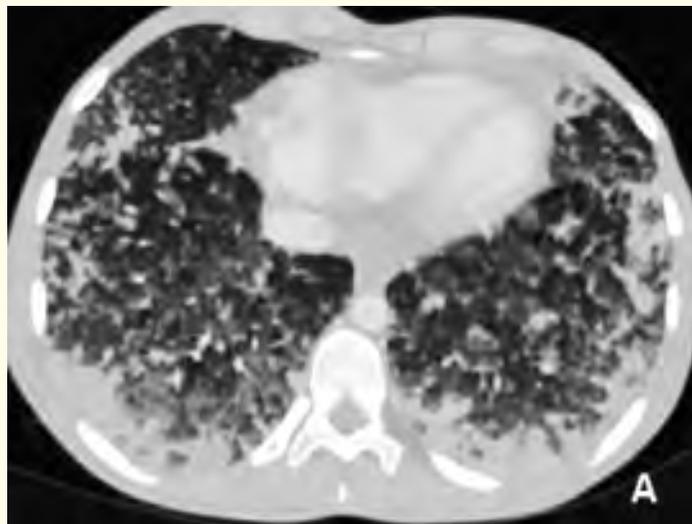


Figure 2: CT axial scan documented hepatization of both lungs (a) and right pleural effusion (b).

Discussion and Review of the literature

The reported cases of KHE in the adult were few and in the most of them the localization were extracardiac (Table 1), the cardiac hemangioendotheliomas described in the literature were the histological type “epithelioid” (Table 2).

Histopathologic features of KHE include: infiltrating nodules/sheets of variably spindled endothelial cells, focal immunopositivity for lymphatic endothelial markers, slit-like vascular channels, absence of mitosis or nuclear atypia, microthrombi, hemosiderin deposition, oedema, fibrosis, and abnormal lymphatic channels [28] (Figure 3-4).

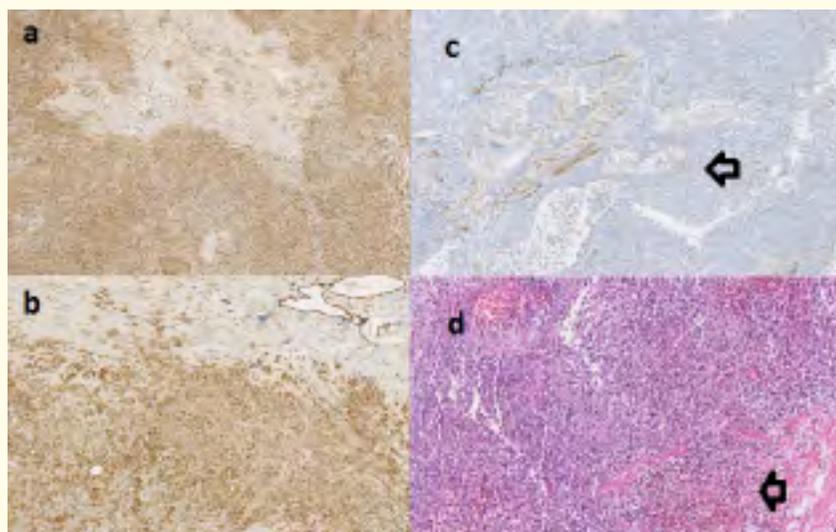


Figure 3: Histopathological characteristics: Cardiac Kaposiform hemangioendothelioma (CKHE) solid aggregations of poorly canalized slit-like capillaries lined with spindle cells and containing blood red cells (immunohistochemistry with CD31 antibody, (a)×25 and (b)×40). The Histological examination of the primary cardiac tumor revealed a proliferation of spindle large epithelioid and glomeruloid tumor cells presenting atypical features (arrow). Hematoxylin-eosin-saffron (c, x 10) and smooth muscle Actin staining (d, x 40).



Figure 4: Immunohistochemistry with epithelial membrane antigen (EMA) antibodies to highlight the infiltrate area in lungs (a) and myocardium (b).

All of the 34 cases reviewed in this study were confirmed histopathologically by surgical removal, biopsy or autopsy. Patient age ranged from 20 to 93 years, the average age was 55.43 years (Figure 5). Females were predominant gender (54.5%). Early diagnosis were only in 11 cases (33.3%) and 22 (66.7%) were misdiagnosed as other tumor. The localizations of the tumor were different (Figure 6): cutaneous (32%), Chest wall, neck, groin and buttock (19%), left thigh (7%), paranasal sinus/nasal cavity (6%), mesentery/ileum (6%), and other sites (30%). In the 24 patients with diagnosis of cardiac hemangioendothelioma reported in the scientific literature (Table 2), the principal cardiac site was right atrium (41.7%) and the histological pattern was epithelioid in all.

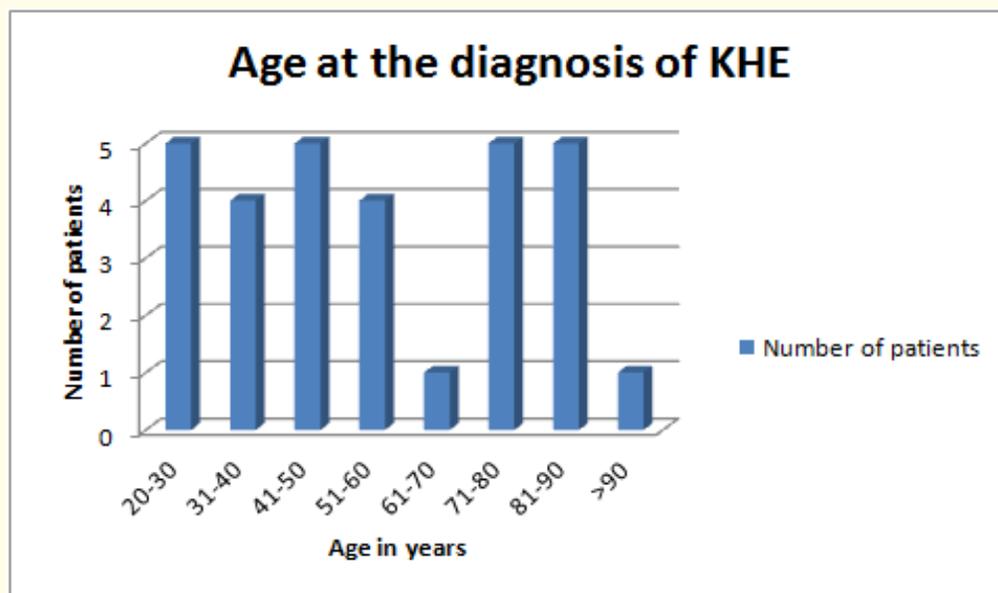


Figure 5: Age at the diagnosis of Kaposiform Hemangioendothelioma (KHE).

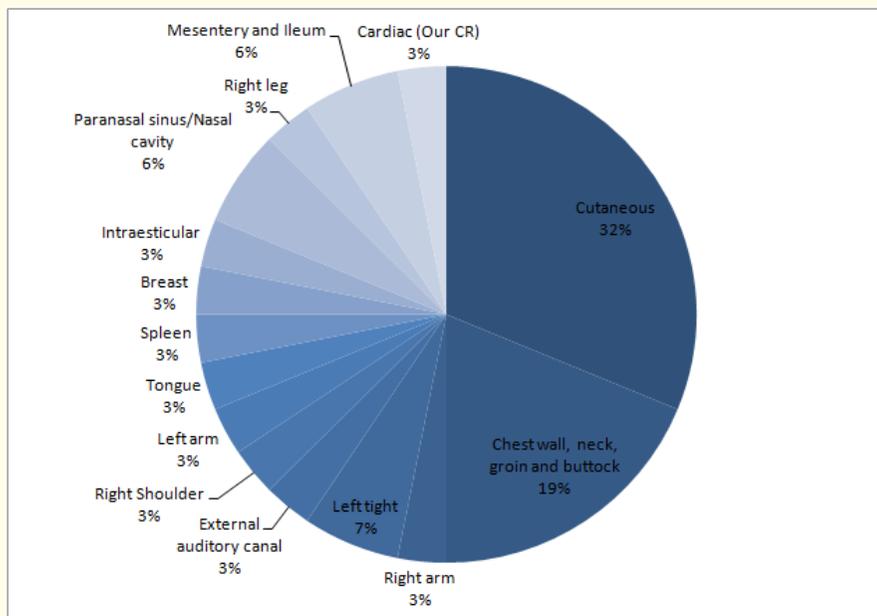


Figure 6: Primary localization of the KHE in the 34 reviewed cases.

The histological assessment of KHE was characterized by areas of spindle cells with slit-like vascular spaces, hyaline globes, hemosiderin deposition and areas of epithelioid endothelium in glomerular nests (Figure 7). These features were commonly associated with the Kaposi sarcoma. On the contrary, KHE was never associated with the human herpes virus-8 infection, which instead was always associated with the Kaposi sarcoma. The endothelial cells reveal typical vascular markers, such as CD31,CD34, and were negative for GLUT-1 [32] (Figure 4).



Figure 7: The histological assessment of KHE by areas of spindle cells with slit-like vascular spaces, hyaline globes, hemosiderin deposition and areas of epithelioid endothelium in glomerular nests.

According to our comprehensive analysis, the most of the patients were CD31 and CD34 positive (30.3%) and CD 99 positive (18.1%).

Treatment of KHE requires a multimodal therapeutic approach (Table 3). The medical treatment was based on steroids [34,70,71], vincristine [34,35,66,67,70,77], aminocaproic acid [65], thalidomide [38,64], interferon alpha [36,39,48], less commonly on cyclophosphamide [68], actinomycin-D and thalidomide [64], bevacizumab [40,71], recently radiation therapy [36,37,48,50,62,71], sirolimus [67,76], everolimus [70,73], paclitaxel [63], propranol [74]. Surgery should be considered for small lesions or tumors which were unresponsive to medical treatment (Table 3). The 44% of the reviewed cases were treated by surgery, 8 patients (30%) by irradiation, 5 patients (18%) by drug injection (IL-2 or interferon alpha-2B), and 2 patients (8%) by combined therapy (Figure 8).

Principal Reported Therapeutic Choice in Kaposiform Hemangioendothelioma			
Therapy	Author	Dose	Effect
Aminocaproic acid	Wallestein., <i>et al.</i> [65]	4-5 g IV/PO during 1st hr, THEN 1-1.25 g PO q1hr, OR Continuous IV infusion at 1 g/hr	Inhibitor of proteolytic enzymes like plasmin and the enzyme responsible for fibrinolysis
Bevacizumab	Trautmann., <i>et al.</i> [40] Barabasch., <i>et al.</i> [71]	5-10 mg/kg IV	directly binding to VEGF extracellularly to prevent interaction with VEGF receptors (VEGFRs) on the surface of endothelial cells
Cyclophosphamide	Gu., <i>et al.</i> [68]	60-120 mg/m ² /day (1-2.5 mg/kg/day) IV	An alkylating agent adds an alkyl group to DNA., and attaches the alkyl group to the guanine base of DNA, at the number 7 nitrogen atom of the imidazole ring.
Everolimus	Fernandez., <i>et al.</i> [70] Matsumoto., <i>et al.</i> [73]	0.1 mg/kg/day	Inhibitor of mammalian target of rapamycin
Interferon α- 2B	Hesselmann., <i>et al.</i> [36] Mac-Moune Lai., <i>et al.</i> [48]	3 MIU/m(2)/day	Immunomodulatory effect by regulating the cytokines that control the function and reproduction of tumour cells.
Intralesional injection of absolute ethanol	Yuan., <i>et al.</i> [66]	/	For the cutaneous kaposiform lesions
Paclitaxel	Grellety., <i>et al.</i> [63]	135 mg/m ² IV over 3 hours 3Weeks; or 100 mg/m ² IV over 3 hours 2Weeks	Specific binding site on the microtubule polymer and stopping polymerization of tubulin
Propranolol	Hermans., <i>et al.</i> [74]	/	In association with vincristine
Radiation therapy	Hesselmann., <i>et al.</i> [36] Scott., <i>et al.</i> [37] Mac-Moune Lai., <i>et al.</i> [48] Hardisson., <i>et al.</i> [50] Dong., <i>et al.</i> [62] Barabasch., <i>et al.</i> [71]	/	/
Corticosteroids	Drucker., <i>et al.</i> [34] Fernandez., <i>et al.</i> [70] Barabasch., <i>et al.</i> [71]	2 mg/kg	Be careful to existing steroid-resistance of KHE
Surgery	O'Rafferty., <i>et al.</i> [67] Hardisson., <i>et al.</i> [50] Chu., <i>et al.</i> [51] Bienaimé., <i>et al.</i> [52] Vetter-Cauczok., <i>et al.</i> [53] Yu., <i>et al.</i> [55] Kim., <i>et al.</i> [56] Costa., <i>et al.</i> [57] Wu., <i>et al.</i> [58] Wong., <i>et al.</i> [59] Zang., <i>et al.</i> [61] Maseda., <i>et al.</i> [75]	/	Excision (partial, total, and so on), Cyberknife
Sirolimus	O'Rafferty., <i>et al.</i> [67] Oza., <i>et al.</i> [76]	0.8 mg/m ²	Directed against the PI3/AKT/mTOR downstream signalling pathway involved in lymphangiogenesis
Thalidomide	Lisle., <i>et al.</i> [64]	/	Anti-angiogenic
Ticlopine	López., <i>et al.</i> [33] Fernandez., <i>et al.</i> [70] Barabasch., <i>et al.</i> [71]	/	In association with vincristine and aspirin
Vincristine	Drucker., <i>et al.</i> [34] Fahrtash., <i>et al.</i> [35] Yuan., <i>et al.</i> [66] O'Rafferty., <i>et al.</i> [67] Fernandez., <i>et al.</i> [70] Subash., <i>et al.</i> [77]	1mg/m ² /week	Anti-platelet therapy, especially used in steroid resistant KHE with KMP

Table 3: The principal therapeutic choices for kaposiform hemangioendothelioma documented in scientific literature. IV: Intravenous; PO: Oral Posology; VEGF: Vascular Endothelial Grow Factor; mg: Milligram; kg: Kilogram; MIU: Million International Units; KHE: Kaposiform Hemangioendothelioma; PI3: Phosphatidyl Inositide-3; AKT: Protein Kinase B; mTOR: Mammalian Target of Rapamycin; KMP: Kasabach-Merritt Phenomenon.

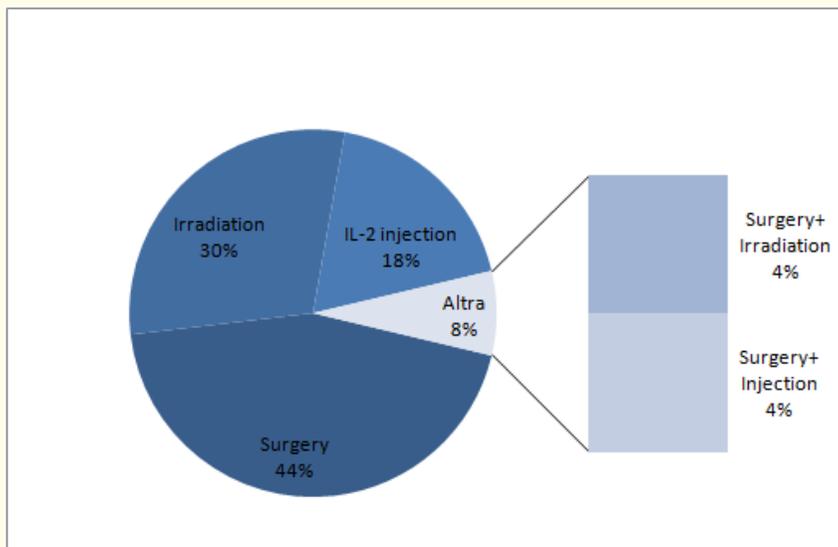


Figure 8: Therapeutic choices of KHE documented in the 33 reviewed cases.

In our case, the first diagnostic suspect had been infective because of the prevalence of respiratory symptoms (fever, cough, hemoptysis, and alveolar hemorrhage) because young patient with unremarkable medical history. But the development of acute respiratory distress syndrome (ARDS) requiring veno-venous ECMO and the coagulative disorders, associated with the persistent low platelet count and airway bleeding addressed us to the suspicion of KHE and Kasabach-Merritt phenomenon (KMP). The advance end-stage of KHE and KMP were fatal for the patient.

Several factors should influence the outcome of patients with KHE: early diagnosis, patient clinical condition, accessibility to surgical excision, location (cutaneous versus visceral), size of mass, clinical response to interferon and steroids (glucocorticoids), and the absence of lymphangiomatosis and KMP [43,44]. KMP was a severe thrombocytopenia resulting from intralesional platelet trapping [28,41], firstly describing in the 1940 as “extensive purpura” complication of “capillary haemangioma” [30]. Thrombocytopenia, resulting from platelet trapping within the tumour, was always severe and accompanied by decreased fibrinogen and elevated levels of D-dimer. Those particular biological features of KMP must be differentiated from the clotting disorder associated with extensive superficial or visceral venous or lymphatico-venous malformations [42,43].

Conclusion

Primary cardiac kaposiform hemangioendothelioma was a rare, malignant and sporadic vascular tumor in the adult. Most commonly Cardiac KHE was documented in infants and children such as it was reported by Walsh., *et al* [78]. The scientific literature is lacking of primary cardiac kaposiform hemangioendothelioma in the adult. Although extremely rare, cardiac KHE had to be considered in the differential diagnosis of a solitary cardiac mass. Location, size, rate of growth, biological and clinical features of these tumours strongly differ from those of similar lesions in other part of the body. Early diagnosis, extensive tumour removal, opportune indication of adjuvant treatment with radiotherapy and chemotherapy could be the keys to manage these cases in addition to accurate and continuous control of coagulation profile.

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Conflicts of Interest

All the authors declare non conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revisions.

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