Epithelioid hemangioendothelioma: an overview and update on a rare vascular tumor

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Abstract

Epithelioid hemangioendothelioma is a rare vascular tumor, described for the first time in 1975 by Dail and Liebow as an aggressive bronchoalveolar cell carcinoma. The etiology is still a dilemma. Studies about suggestive hypothesis are ongoing. Most of the times it affects lung, liver and bones, although this kind of tumor may involve the head and neck area, breast, lymph nodes, mediastinum, brain and meninges, the spine, skin, abdomen and many other sites. Because of its heterogeneous presentation, as it represents less than 1% of all the vascular tumors, it is often misdiagnosed and not suitably treated, leading to a poor prognosis in some cases. Over 50-76% of the patients are asymptomatic. A small number of them complains respiratory symptoms. Bone metastases might cause pathological fractures or spine compression, if they arise in vertebrae. Imaging is necessary to determine morphological data, the involvement of surrounding tissues, and potentially the cleavage plan. It is important to recognize the expression of vascular markers (Fli-1 and CD31 are endothelial-specific markers), and the microscopic evidence of vascular differentiation to make a correct diagnosis, as many pulmonary diseases show multiple nodular lesions. Because of its rarity, there is no standard for treatment. We focused on radiotherapy as a good therapeutic option: despite the poor prognosis, evidence is in favor of radiotherapy which offers local pain control with good tolerance and better quality of life at least at a one-year follow-up in most of cases. Further studies are needed to establish the standard radiation dose to be used for locoregional control of such a complex and extremely rare disease.

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Introduction

Epithelioid hemangioendothelioma (EHE) is a rare vascular tumor with an epithelioid and histiocytoid appearance, originating from vascular endothelial or pre-endothelial cells. It represents less than 1% of all vascular tumors and was described for the first time in 1975 by Dail and Liebow as pulmonary EHE (P-EHE).[1] Initially, it was believed to be an aggressive form of bronchoalveolar cell carcinoma, invading adjacent blood vessels and small airways, hence the name *intravascular bronchioloalveolar tumor*.[2-4]

The term *epithelioid hemangioendothelioma* was introduced in 1982 by Weiss and Enzinger to describe a vascular tumor of bone and soft tissue showing features between hemangioma and angiosarcoma.[5,6] Corrin *et al.* demonstrated the presence of tumor cells deriving from a lineage capable of differentiation along endothelial lines by using immunohistochemical techniques.[7] Later, Weldon-Linne *et al.* confirmed these findings using electron microscopy and revealed a diffuse cytoplasmic staining of the malignant cells with a factor VIII-related antigen.[8]

The recent World Health Organization (WHO 2002) classification describes EHE as lesions that fall into the category of locally aggressive tumors with metastatic potential.[9,10]

The estimated prevalence of EHE is less than one in 1 million.[11] Due to its rarity, with only approximately 248 cases of P-EHE reported in the current literature, few different groups have published large studies (Amin 93 patients,[12] Bagan 80 patients,[13] Kitaichi 21 patients,[14] Dail 20 patients[4]) (Table 1).[12-36] Clinical registries such as the Armed Forces Institute of Pathology Registry and the International Hemangioendothelioma, Epithelioid Hemangioendothelioma and Vascular Disorders Registry may help in following the natural history of the disease.[37]

The majority of patients were females (male:female 1:4) in most of the studies about P-EHE (Amin 73%, Bagan 65%, Kitaichi 62%, Dail 80%), while pleural EHE seems to be more frequent in males.[38] This malignant vascular tumor usually affects middle-aged patients,

although cases in children and elderly people have been described. The age of the patients ranges from 7 to 83 years old.[15,16] The median onset is 36 years old, while the usual age at diagnosis is from 20 to 60 years old.[17]

Etiopathogenesis

The etiology of EHE is still a dilemma. At the molecular level, different angiogenic stimulators may act as promoters of endothelial cell proliferation.[18] Recently it has been reported that monocyte chemo-attractant protein-1 is required for EHE proliferation and might promote the development of these lesions by stimulating the angiogenic behavior of endothelial cells.[39] Budousquie *et al.* described several clonal abnormalities in tumor cells: a complex unbalanced translocation between chromosomes 7 and 22 with multiple breakpoints, a robertsonian translocation of chromosome 14, and the loss of chromosome Y.[40] Monosomy for chromosome 11 and thetraploidy have also been detected in a subset of tumor cells. Errani *et al.* focused on the t(1;3) (p36.3;q25) mutation: a molecular analysis revealed that CAMTA1 on chromosome 1p36.23 and WWTR1 on chromosome 3q25 are the involved genes. Both genes had previously shown to play important roles in oncogenesis, but it is the first time they are implicated together in a recurrent chromosomal translocation, in EHE. Particularly important is just the lack of CAMTA1 and WWTR1 rearrangements in *epithelioid hemangioma*, a benign tumor that is often misdiagnosed as EHE.[41] Recently, Antonescu *et al.* have found *YAP1* rearrangements in most of the transcription factor E3 (TFE3)-rearranged EHEs, and this YAP1-TFE3 fusion subset occurs at the mean age of 30 years showing at least focally, well-formed vascular features and a variably solid architecture.[42]

A new, suggestive hypothesis of the pathogenesis of this disease refers to a causal relationship between chronic *Bartonella* infection and the development of this rare vascular tumor. The unique Bartonella's capability of invading and inducing long-lasting intraerythrocytic and intraendothelial infections, together with the ability of at least three *Bartonella* spp. (*B. henselae*, *B. quintana*, *B. bacilliformis*) of inducing vascular endothelial growth factor-mediated vasoproliferation, as they upregulate mitogen and proinflammatory genes resulting in cytoskeletal rearrangement and suppression of endothelial cell apoptosis, suggest that these bacterial pathogens might contribute to the development of vascular tumors.[43]

Occurrence and metastasis

The Hemangioendothelioma, Epithelioid Hemangioendothelioma And Related vascular Disorders (HEARD) Support Group observed that the most common EHE presentations are liver alone (21%), liver plus lung (18%), lung alone (12%) and bone alone (14%)[11] (Figure 1). However, EHE is a very heterogeneous tumor, and it has been reported to involve many other sites[44-56] (Table 2). When these cases occur, it may be difficult to determine if the tumor is multicentric or if it is a primary lesion with metastases in other tissues, as EHE may originate in either organ and metastasize to the other or it may have more than one primary site. Sometimes we are able to distinguish metastases from a multicentric primary tumor because of their less differentiation and loss of the expression of epithelial markers.[57]

P-EHE dissemination may occur within blood vessels, lymphatics and pleural cavity. The lung airspaces spread is continuous. Distant hematogenous metastases have been reported mainly in the liver but also in the skin, serosa, spleen, tonsils, retroperitoneum and kidney; colonic metastases have also been described, but they are very rare.[58]

Bone metastases are doubtless the most frequent and the most clinically severe. According to World Health Organization (WHO) classification of Tumors of bone and soft tissues (2002), one half to two thirds of them originates from a vessel (such as a small vein). Exceptionally it may originate from a large vein or artery.[59]

Clinical aspects

The clinical aspects of P-EHE are summarized in Table 1. P-EHE is often incidentally diagnosed and over 50-76% of patients are asymptomatic, usually detected by abnormal chest radiography during health examinations, or they have only minor, aspecific symptoms at the time of the diagnosis. Otherwise, respiratory symptoms together with chest pain or pleuritic pain are typical at P-EHE detection, even if few patients may complain alveolar hemorrhage, hemoptysis and anemia, occasionally clubbing and weight loss.[12-14,20] Table 3 summarizes the clinical aspects of EHE localized at other sites, different from lung: the clinical presentation of this rare vascular tumor is as heterogeneous as its clinical localization can be.[2,10,47,49,51,53-58,60-69] In particular, when bone metastases of EHE involve more than 50% of the cortex, there is a serious risk for pathological fractures, and if they arise in vertebrae they might cause spine compression and therefore paresthesia, loss of muscular strength and paraplegia.[57,60,61] Hemolytic anemia and consumption coagulopathy have been rarely described. Usually, male P-EHE patients tend to be detected more frequently by subjective symptoms (50%) than females (8%).[11]

Diagnostic tools

Laboratory data

Blood counts are usually normal. There is no effect on the total white blood cell count, erythrocyte sedimentation rate or serum proteins, but several values might abnormally increase if the liver is involved: white blood cell count, serum alkaline phosphatase, aspartate aminotransferase, gammaglutamyl transferase, amylase and lipase.[63] Chemistry profiles and urinalyses are generally normal.

Radiological findings

The imaging evaluation of the EHE must be as complete as possible. The radiology examination and magnetic resonance imaging (MRI) are necessary to obtain morphological data: the degree of the neoformation, the relations with the surrounding tissues, a potential cleavage plan.[61]

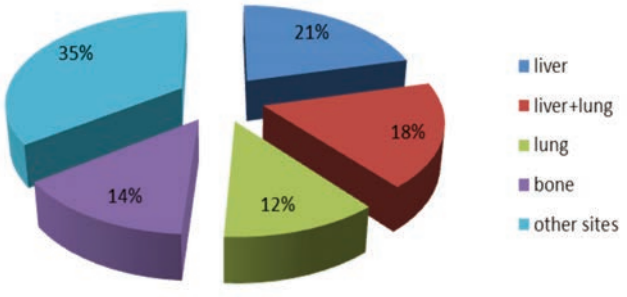

Figure 1. The most common epithelioid hemangioendothelioma presentations.

Table 1. Summary of the pulmonary epithelioid hemangioendothelioma cases reported in the current literature.

Author/Reference	No.	Gender M/F	Age at detection	Pulmonary nodules	Therapy	Metastatic spread	Survival years	Clinical presentation
Dail[4]	20	4/16	36	Bilateral	Surgery	Liver (3/20)	4.6-6.4	Incidental in many cases
Amin[12]	93	25/68	40.1	Multiple bilateral or unilateral	Surgery CHT None	Liver Pleural Lymph node metastases Bone	5-year survival curves 30-90%	No symptoms 49.5% Dyspnea 18.3% Cough 18.3% Chest pain 16% Hemoptysis 6.5% Weight loss 6.5% Others 9.7%
Bagan[13]	80	31/49	39.7	Multiple bilateral, unilateral	Surgery Surgery+CHT Radiation None	Liver Bone Brain Bowel	5-year survival 60% (47-71%)	Incidental 48.7% Respiratory symptoms 42.5% Hemoptysis 11.2% Weight loss 6.2% Abdominal symptoms 2.5% Anemia
Kitaichi[14]	21	8/13	44	Bilateral or unilateral	Surgery CHT (mitomycin C, 5FU, cyclophosphamide, vincristine, tegafur) None	Liver Bone	0.5-12 years (81%) Partial spontaneous regression (14.3%)	Dyspnea 9.5% Cough 28.6% Sputum 9.5% Chest pain 19% No symptoms 76%
Rock[15]	1	0/1	7	Bilateral	Not stated	Liver	Not stated	Pleural thickening
Einsfelder[16]	11	4/7	49.8	Multiple bilateral	Surgery CHT Interferon-2α None	Liver Pleural Bone Meningeal Peritoneum	6-105 months	Not stated
Schattenberg[17]	3	1/2	47.3	Multiple bilateral	Surgery CHT (ifosfamide+ adriamycin) Radiation None	Liver (1/3)	24 months (suicide) 36 months (alive) 16 months (alive)	Chronic thoracic pain 3/3 Prickling sensations of the left arm 1/3
Radzikowska[18]	1	0/1	62	Multiple bilateral	Interferon-2	None	6 months (then lost at observation)	Cough Osteo-articular pain
Ye[19]	1	0/1	55	Multiple bilateral	None (refused)	Liver	7 months	Pleuritic pain and irritable cough
Sicilian[20]	1	0/1	Young	Bilateral	Not stated	None	Not stated	Not stated
Teo[21]	1	0/1	40	Radiological abnormalities	Not stated	Not stated	20 years	Not stated
Miettinen[22]	1	0/1	17	Bilateral	Surgery	Retroperitoneum	24 years	Not stated
van Kasteren[23]	1	1/0	10	Bilateral	Radiation CHT (doxorubicin)	Bone Liver	21 years	Dyspnea
Gaur[24]	1	1/0	35	Multiple bilateral	Palliative radiation CHT (bevacizumab + nab-paclitaxel +zolendronic ac.)	Superior and anterior mediastinum Bone	Not stated (stable disease at 6-month-follow up)	Cough Shortness of breath Chest wall, lower back and both legs pain Weight loss (10 kg)
Nakatani[25]	1	1/0	68	Bilateral	Not stated	Liver	Not stated	Not stated

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Table 1. Continued from previous page.

Author/Reference	No.	Gender M/F	Age at detection	Pulmonary nodules	Therapy	Metastatic spread	Survival years	Clinical presentation
Yanagawa[26]	1	0/1	Not stated	Not stated	Not stated	Skin	Not stated	Not stated
Coulibaly[27]	2	1/1	41	Multiple bilateral	Not stated	None	9 months (alive)	Chronic cough
							7 months	Worsening dyspnea Expectoration Hemoptysis
Hanada[28]	1	1/0	45	Unilateral	None	None	66 months	No symptoms
Cronin[29]	1	0/1	35	Bilateral	-	None	9 months	Shortness of breath and dry cough
Sakamoto[30]	2	1/1	36	Multiple bilateral	Not stated	Liver (2/2)	Not stated	Not stated
Iwashima[31]	1	0/1	51	Bilateral multiple nodular shadows	None	None	24 months (alive)	No symptoms
Chen32	1	0/1	58	Bilateral	None Radiation CHT	Mediastinum	20 years	Dyspnea
Carretero[33]	1	1/0	62	Multiple bilateral Infiltrates	Not stated	None	3 weeks	Increasing dyspnea
Anagnostou[34]	1	0/1	36	Multiple bilateral	None	None	24 months	Progressive dyspnea and fever because of associated nocardiosis
Saleiro[35]	1	1/0	39	Multiple bilateral	Interferon-2	None	9 months	Pleuritic and right-sided chest pain
Bahrami[36]	1	1/0	37	Left hilar mass	Unresectable Radiation CHT	Pleura Pericardium Diaphragm Skin of the thoracoabdominal wall	11 months	Back pain

CHT, chemotherapy.

P-EHE radiologically appears as multiple perivascular nodules with well-defined or blurred margins in both lungs, showing little or no growth on serial chest radiographs or computed tomography (CTs). The nodules may range in size up to 2 cm, but most are less than 1 cm in diameter and are predominantly in the lower parts of the lungs. They are usually found at small and medium sized vessels and bronchi. Bilateral multiple nodular opacities are the most common presentation: about 60% of cases display these changes, even if P-EHE occasionally develops as a solitary, lung nodule, measuring up to 5 cm (10-19% of cases[13]). Hilar lymph node enlargement, lymph node metastases, interlobular septal thickening and pleural effusions can be also noticed, as well as unilateral opacities and mosaic areas of ground-glass attenuations. Radiologic calcification is not common but histologic examinations often reveal calcified and ossified necrotic centers of the nodules.[29]

Bone metastases appear as osteolytic lesions with homogeneous contrast enhancement on X-ray and CT scan, without matrix mineralization; osseous expansile remodeling may be seen, and joint invasion is also a common feature. These lesions can be localized in the cortical or medullary bone: cortical disruption and extension into the soft tissue can be present, so soft tissue swelling might be radiologically observed in this case. Periosteal reaction is rare in the absence of pathologic fracture, instead, as well as calcification. There is no specific pattern of signal intensity at MRI imaging. Most frequently EHE shows low to intermediate signal intensity on T1-weighted images and high signal intensity on T2-weighted images, together with homogeneous enhancement after the injection of contrast medium.[60]

Ultrasonography emphasizes the tumor's vascularization and allows differential diagnosis *vis-à-vis* an arteriovenous malformation or even an aneurysm.[61]

In some cases, positron emission tomography[17] and bone scintigraphy are used to evaluate lesions at other sites. Increased uptake of F-fluorodeoxyglucose in this tumor has been recently reported.[70-72]

Table 2. Other sites of epithelioid hemangioendothelioma presentations.

Site
Head and neck
Breast
Lymph nodes
Mediastinum
Diaphragm
Brain and meninges
Mastoid
Infundibulum
Clivus
Cerebellopontine angle
Spine
Skin
Peritoneum
Stomach
Retroperitoneum
Ovary
Prostate
Eyelid

Table 3. Summary of the cases of epithelioid hemangioendothelioma of other sites in the current literature.

Author/Reference	No.	Gender M/F	Age at detection	Tumor site	Therapy spread	Metastatic	Survival years	Clinical presentation
Wong[2]	1	0/1	50	Subcutaneous fat of forehead-left orbit-left frontal sinus	Surgery	Frontal bone	Not stated	Red-colored nodular skin lesions Visual disturbance
Mukherjee[10]	2	1/1	20	Anterior abdominal wall	Not stated	None	Not stated	Painful anterior abdominal wall swelling Palpable mass Enlargement of right tonsil
Drazin[47]	1	1/0	62	Mastoid bone	Surgery Radiation	None	8 years (alive)	Positional vertigo Hearing loss Mild mass effect upon the 4th ventricle
Ma[49]	1	0/1	58	Clival region	Surgery	None	Not stated	Pain of the forehead Visual deterioration
Kerry[51]	1	1/0	25	D7	Surgery Adjuvant radiation CHT (doxorubicin)	Lymph nodular and cutaneous	8 weeks	Severe back pain Paraplegia
Iimuro[53]	1	0/1	48	Retroperitoneum	Surgery	Regional and Virchow's lymph nodes	13 months	Slight discomfort in lower right abdomen
Illueca[54]	1	0/1	20	Ovary	Surgery	None	1 year	Pelvic pain
Iyer [55]	1	1/0	69	Prostate	-	Seminal vescicles Periprostatic extension	Not stated	Perineal pain night sweats rectal fullness increased urinary frequency urgency
Al-Faky[56]	1	0/1	27	Eyelid	Surgery	None	Not stated	Eyelid swelling
Gomez-Arellano[57]	1	1/0	19	D1, D3, D4	Palliative radiation	Lung Pleura	5 months	Back pain Paresthesia Loss of strength of lower limbs Pathologic fracture Paraplegia
de Singly[58]	1	1/0	78	D9	Surgery	Colonic metastases	-	Periumbilical pain Weight loss General condition alteration
Larochelle[60]	1	1/0	57	Right ankle-tibia-talus	Surgery	None	Not stated	Right ankle pain Surrounding edematous bone reaction
Gherman[61]	1	1/0	24	Forearm	Surgery	None	24 months	Pain Weakness Oval palpable mass
Vidya[62]	1	0/1	16	Skin of the right lower limb	Surgery	None	Not stated	Swelling Erythematous skin lesions
Kim[63]	1	1/0	47	Liver	Liver transplantation	Infraioid neck	Not stated	Blood count alteration
Aquilina[64]	2	2/0	38.5	C2-4, D10	Surgery Radiation CHT (ifosfamide+ carboplatin+etoposide +vincristine)	None	Not stated	Nocturnal thoracic low-back pain Neck pain

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Table 3. Continued from previous page.

Author/Reference	No.	Gender M/F	Age at detection	Tumor site	Therapy spread	Metastatic	Survival years	Clinical presentation
Pinet[65]	1	0/1	50	Parietal pleura	CHT (carboplatin +etoposide)	Peritoneum	Not stated (complete remission 18 months after CHT)	Right pleural effusion Contralateral pleural effusion Chylous ascites
Kleck[66]	1	1/0	61	Right distal humerus	Surgery	Two local lymph nodes and an ipsilateral axillary lymph node	Not stated Swelling Palpable mass	Severe pain Limited range of motion Decreased strength Pathological fracture
Rosenthal[67]	1	0/1	21	Left foot and mid-leg	RF ablation surgery	Left distal femur Left medial foot Distal left tibia Left 2nd metatarsal	6 years	Left foot and tibial pain
Kabukcuoglu[68]	1	0/1	48	1st metatarsal	Surgery	None	4 years	No symptoms
Sardaro[69]	1	0/1	46	Multiple disseminated pleuropulmonary nodules	Surgery Radiation CHT (ifosfamide+epirubicin)	L3-L4 Spleen	11 months	Back pain

CHT, chemotherapy; RF, radiofrequency.

Histological and cytological features

When EHE was identified, electron microscopy showed a typical image of endothelial cells similar to those composing medium-size vessels, or a large vein, arranging in nests or cords, while immunohistochemistry revealed Weibel-Palade bodies in the cytoplasm of their cells as a typical finding.[64] Table 4 describes the typical macroscopical and histolgical P-EHE appearance.[73] Spindle-shaped tumor cells are occasionally present. The cell growth may form lumens of various size which occasionally contain red blood cells, that is the numerous distinct cytoplasmic vacuoles (ICLs) which may be observed under a microscope. Sometimes the ICLs are so large that the nucleus is compressed, and the cells present a signet-ring appearance.[14,52] Some smears have been reported to contain cells arranged as single cells and pseudopapillary and pseudoglandular structures of varying size, or complex branching cell groups with central stromal cores, as well as cell aggregates lacking sharp anatomic borders or scalloped outlines. At the nodule's peripheral region the tumor cells extend to adjacent alveoli through the pores of Kohn, in the form of a micropolypoid growth into the lumen of respiratory and membranous bronchioles. However, the alveolar elastic framework is essentially preserved, as demonstrated by the presence of elastic tissue stains. The neoplastic tissues may invade the walls and the lumens of small pulmonary arteries, veins and lymphatic vessels. Inflammatory cellular infiltrate, congestion in the adjacent lung parenchyma and fibrin thrombosis are usually not seen. The Kitaichi's study with a detailed biological description of the 21 P-EHE patients analyzed and well categorized all these histopathological features[14] (Table 5).

Immunohistochemistry

A variety of endothelial proteins may be useful to identify EHE. The Fli-1 protein is expressed by the endothelium as well as the T-cells and megakaryocytes: this nuclear protein has proven useful in identifying vascular neoplasm including EHE, showing a better combined sensitivity and specificity than the endothelial markers CD31 and CD34. CD34 is reported to be expressed by more than 90% of vascular tumors, so this marker has poor specificity as a variety of soft tissue tumors also express it. In contrast, CD31 is regarded as a relatively specific vascular tumor marker. Some authors maintain that the combination of Fli-1 and CD31 represents an ideal panel for the differential diagnosis.[74] Podoplanin is specifically expressed by lymphatic endothelial cells and has been reported to be a useful diagnostic marker to identify EHE in the liver. In addition, few cases of EHE show weak and focal positivity for cytokeratin, so cytokeratin expression does not seem to be specific for epithelial origin.[74] Positive EMA and CD68 have been reported in bone EHE,[9] while a case of prostatic EHE showed positive p63 and PSA plus weak patchy immunoreactivity for pankeratin (negative for urothelial markers instead, as opposed to prostatic adenocarcinoma).[55] In this regard, the endothelial marker ERG is worth a mention: this is an ETS family transcription factor which is known to be expressed in endothelial cells, whose oncogenic *ERG* gene fusions occur in subsets of prostatic adenocarcinoma, acute myeloid leukemia and Ewing sarcoma. Miettinen *et al.* reported ERG to be expressed over the endothelia of all of the hemangiomas, lymphangiomas and Kaposi sarcomas they analyzed, 96% of angiosarcomas and 42 of the 43 cases of EHEs they included in their study.[75]

Prognosis and death causes

The mean survival is 4.6 years, ranging from 6 months to 24 years.[11,21,22] Gomez-Arellano *et al.* reported that mortality is 13% when

EHE is located in soft tissue, 35% when it affects the liver, and 65% if it reaches the lung. According to the Kenneth Lau analysis, the 1-year-overall survival (OS) is 90% (73% the 5-year-OS), while the 1- and 5-year-OS after EHE progression is 53% and 24%, respectively (median survival 1.3 years after disease progression).[11,57] Asymptomatic P-EHE patients have a median survival of 180 months. Some cases of partial spontaneous regression were also reported in some asymptomatic patients. The median onset is statistically worse in case of alveolar hemorrhage, hemoptysis, hemorrhagic, pleural effusion, anemia (OS<1 year according to the Bagan's study).[13] Patients with hilar metastases or liver involvement were also reported to have a worse prognosis, with an average survival of 2.2 years.[17] EHE progresses on average in 2 years (range 0.3-22.3 years), but the presence of metastasis at the time of diagnosis does not necessarily correspond with reduced survival. Nonetheless concomitant involvement of the skeleton and viscera does not affect survival as long as it is localized and confined. Only multi-organ involvement carries a clear survival disadvantage. Conversely, we may consider the involvement of 3 or more bones and ascites as poor prognostic factors.[11] All this considered, we may define the presence of pulmonary lesions, multi-organ involvement, disease progression, age ≥55 years old, male patients as poor prognostic factors. Patients complaining severe respiratory symptoms (dyspnea, cough, chest pain, hemoptysis and alveolar hemorrhage), weight loss and anemia are also statistically worse, as well as those presenting pleural invasion and pleural effusion on chest X-ray at detection, extensive intravascular, endobronchial or intestinal tumor spread, hilar metastases or liver involvement, peripheral lymphadenopathy, extensive lymphangitic spread. Finally, histological finding as spindle tumor cells, fibrinous pleuritic lesions or extrapleural tumor cells proliferation show a trend towards a worse prognosis.[4,13,14,17,19,76]

Most patients die from respiratory failure as a result of tumor nodules increasing in size and number. In patients with bilateral disease, those with radiologic findings of alveolar hemorrhage (interstitial lesions, ground glasses opacities) and those with hemorrhagic effusion, a rapid respiratory failure is usually the cause of death.[13] A small group succumbs because of extrapulmonary spread of tumor, with a predominance of liver and bone disease.[23]

Differential diagnosis

There are many pulmonary diseases presenting with multiple nodular lesions, including hematogenous metastases, pulmonary arteriovenous malformations, granulomatous infections and granulomatous diseases such as pulmonary hyalinizing granuloma, Wegener's granulomatosis and sarcoidosis, non-Hodgkin's lymphoma, pneumoconiosis, multiple hematomas, amyloidosis, multiple calcifying fibrous tumors (CFT).[22] Also pneumocytoma, formerly known as sclerosing hemangioma of the lung, has to be differentiated from P-EHE: it is a benign lung neoplasm and was described for the first time by Liebow and Hubbel, showing an epithelial origin with dedifferentiation of type II pneumocytes (hence the name *pneumocytoma*).[77,78]

Cytologic features, together with immunohistochemistry analysis (especially the expression of vascular endothelial markers), allow to differentiate them: negative Congo Red (different from amyloidosis), non-specific inflammatory infiltration (granulomatous disease), dense hyalinized collagenous tissue with psammomatous and lymphoplasmacitic infiltrates (CFT).[79] The histologic evaluation is also necessary for differential diagnosis between EHE and other epithelioid tumors, such as adenocarcinoma (whose cytoplasmic vacuoles do not contain erythrocytes - positive for mucin stains, instead - as well as diffuse positivity for cytokeratin and epithelial membrane antigen); malignant mesothelioma (showing little cytologic atypia, two-toned cytoplasm known as fuzzy cytoplasmic borders, lack of cytoplasmic vacuoles, positivity for mesothelial markers such as calretinin, cytokeratin 5/6 or WT-1); melanoma (with greater amounts of cytologic atypia and more frequent mitoses, necrotic debris and melanin pigment, and expression of S100 protein, MART-1, and other melanocytic markers); Epithelioid angiosarcoma (presenting greater cellularity, larger cells, more prominent mitotic activity, greater nuclear and nucleolar pleomorphism, and more frequent tightly, cohesive cell clusters without myxohyaline matrix, immunoreactivity for vimentin and cytokeratin); epithelioid sarcoma (negative for vascular markers);[52] meningioma (in case of intracranial localization, negative for vascular markers and positive for cytokeratin and S-100 protein).[49] Sometimes EHE of bone needs to be differentiated from chordoma, chondromyxoid fibroma and myxoid chondrosarcoma, which are more voluminous and positive for S-100 protein.[57]

The presence of the aforementioned cytological features should prompt correlation with clinical, radiologic and histologic features (vascular differentiation), and immunochemical evaluation (vascular markers expression) so as to ensure that the diagnosis is correct.[80]

Treatment options

Because of its rarity EHE has no standard for treatment, and actually few therapeutic options are available. If the proposed association of *Bartonella* spp. infections were confirmed, it would be plausible that eradicating the bacterial infection or interrupting *Bartonella*-induced angiogenic and proliferative cell signals could slow the tumor progression and improve patient outcomes.[43]

Table 4. Pulmonary-epithelioid hemangioendothelioma histological and cytologic features.

	Solitary or multiple pulmonary nodules
Macroscopical appearance	
Diameter	>5 cm
Consistency	Rubbery or cartilage-like
Cut surface	From grey-white to yellow-brown Semi- or normotranslucency
Microscopical appearance	
Periphery of the nodules	Hypercellular
Centre of the nodules	Hypocellular Coagulative necrosis Hyalinization Calcification Ossification
Cytoplasm	Abundant
Nucleus	Round or oval
Atypia	Low-grade, one third marked
Mitotic activity	Scarce, one third notable (>10 mitosis/HPF)
Increased risk of metastasis	
	Marked nuclear atypia Notable mitotic activity (>10 mitosis/HPF) Necrosis

HPF, high-power fields.

Table 5. Histopathological features of pulmonary-epithelioid hemangioendothelioma in 21 patients.

Cellularity		Grade 1 17	Grade 2 2	Grade 3 0	-	-
Spindle tumor cells	Grade 0 Absent 8	Grade 1 Mild 11	Grade 2 Moderate 2	Grade 3 Marked 0	- -	- -
Nuclear polymorphism		Mild 16	Moderate 5	Marked 0	-	-
Necrosis of neoplasm % of necrotic changes	Grade 0 None 4 (19%)	Grade 1 Minimal 1 (5%)	Grade 2 <25% 3 (14%)	Grade 3 25-50% 2 (10%)	Grade 4 50-75% 6 (29%)	Grade 5 >75% 5 (24%)

The available treatment options are mentioned in Tables 1 and 3. When the lesions are small and limited in number, some authors recommend surgical resection or an preventive approach to asymptomatic patients. Successful curative resection achieves good outcomes. The role of adjuvant chemotherapy and/or radiation therapy (RT) is ambiguous, instead. Usually RT after surgical resection is chosen for localized EHE, in order to control the residual disease given the recurrence of EHE, while chemotherapy is preferred in case of widespread disease. However, their beneficial effect is still not confirmed.[4,14,17,23,65]

Lung

In patients with unilateral P-EHE nodules, wedge resection offers the same survival outcomes as anatomic resection does. Hilar lymph node resection should be systematically proposed, but the prognostic value of lymph node invasion remains statistically unclear because of the low number of patients with lymph node metastases.[13] Conversely, a complete surgical resection is usually impossible for pleural EHE. Pinet *et al.* reported a case of an aggressive form of pleural EHE resulting in complete remission after treatment with carboplatin plus etoposide.[65] In patients with bilateral nodules, partial or complete response has been reported using interferon 2 (showing anti-angiogenic properties), and some partial spontaneous regression has also been described.[18] Corticosteroids, azathioprine, multiple wedge resections or simple follow up are the other proposed treatment options. Multiple chemotherapeutic regimens (MAID) have been tried, but no improvement has been reported. Given its vascular origin, angiogenesis inhibition may be a reasonable approach for the management of metastatic EHE. The available literature reported good tolerance and stabilization of an aggressive, metastatic P-EHE using bevacizumab and nanoparticle albumin-bound paclitaxel (nab-paclitaxel): one partial response, one stable disease (that was the only EHE of bone *vs* five P-EHE), and four progression disease (PD) of six patients treated using bevacizumab combined with MAID.[24] In contrast, the use of thalidomide for non-thoracic EHE led to two partial responses, one stable disease and two PD of five treated patients, while using lenalidomide alone resulted in stable disease at the 48-month follow up.[24]

Liver

Locally advanced hepatic EHE seems to benefit from transplantation, with good results.[63]

Bone

Radical surgery is performed for resectable bone tumors, followed by joint reconstruction. *En-bloc* resection is preferred in case of solitary lesions; amputation is necessary for multicentric lesions. When a pathological fracture occurs, temporary internal stabilization with a plate and screws for pain control is chosen.[66] A great alternative in the last case is radiofrequency ablation: the aim is to create small thermal injuries of bone carefully controlled, so that the extent of resection is reduced with a better esthetic result as amputation can be avoided.[67]

Radiation therapy

This therapeutic option has proven to be ineffective for P-EHE because of the tumor's slow growth and consequently of its radiobiological characteristics, while a good local control has been obtained in EHE with exclusive bone presentation when RT was combined with bone surgery, especially if the lesions are not surgically accessible.[23,64]

Since EHE has been correctly defined, there have been several research groups dealing with EHE irradiation. A 4000 cGy for 4 weeks protocol, and later a 3000 cGy course of RT towards the spine after surgical removal of EHE of vertebrae have been described.[23,64] The aim was avoiding local recurrences: 1 case survived 11 years, the remaining ones experienced a worsening due to multiple hepatic and abdominal metastases. Thereafter, a 6400 cGy adjuvant RT was performed against an axillary form of EHE, resulting in the absence of lymph nodes metastases but pleural and pulmonary widespread.[17] A local irradiation after surgical resection of EHE of bone, based on 6000 cGy in 23 fractions for 43 days, showed a good tolerance of the treatment, either regional nor distant metastases or local recurrence at 6, 12 and 24 month-follow-up.[61] A protocol of 33 fractions of RT, totaling 5940 cGy, was recently applied to residual, postoperative mastoid: eight years after surgery and adjuvant RT, imaging has demonstrated neither recurrence nor changes in patient's clinical exam.[47] RT may be used above all in an attempt to sclerose the blood vessels, in any case the use of radiation must be carefully considered in the pediatric age, as RT increases the risk of secondary sarcoma.[68]

Conclusions

Except for P-EHE, taking into account the extremely variable EHE occurrence and its radiobiological characteristics, RT seems to carve out a significant role in the treatment of such a complex and extremely rare disease.

The available literature reveals no consensus about the radiation dose to be used for the locoregional control of EHE: is this attributable to the very small number of patients and to the limited survival that EHE typically shows? Further studies are needed to answer the question. Actually, no doubt evidence is all in favor of RT obtaining local pain control with good tolerance and better quality of life at least at one-year-follow up.

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