Chapter 7
Epithelioid Hemangioendothelioma

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7.1 Definition and Bio-Pathologic Diagnosis

7.1.1 A Recently Identified Malignancy

Epithelioid hemangioendothelioma (EHE) is a recently described, very rare vascular tumor constituting less than 1% of vascular tumors. Nosology definitions were established between the 1970s and 1980s. EHE can arise in soft tissue, viscera (mainly liver or lung) or bone. In 1975, Dail and Liebow had initially described the first case of pulmonary EHE as an aggressive form of bronchioloalveolar carcinoma that massively infiltrates blood vessels and small airways and named this entity "intravascular bronchioloalveolar tumor" [1]. Vascular invasion and infiltrating growth patterns remain of major importance for the diagnosis of EHE. Later, Weiss et al. introduced the term "EHE" to describe a vascular tumor of soft tissue or bone showing features between benign (hemangioma) and malignant (angiosarcoma) [2]. Corrin et al. demonstrated that tumor cells are derived from endothelial progenitors [3], and Weldon-Line et al. showed that the cytoplasm of tumor cells expresses

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factor VII-related antigen [4]. EHEs are positive for other endothelial differentiation markers as well. At the molecular level, chromosomal translocation t(1;3) (p36.3;q25) is a diagnostic marker discriminating EHE (displaying this translocation) from benign epithelioid hemangioma (negative for this marker) [5]. In the current World Health Organization/International Agency for Research on Cancer classification, EHEs are considered locally aggressive tumors with metastatic potential [6].

7.1.2 Criteria for Diagnosis

Macroscopy

– Presence of an angiocentric mass emanating from the vessel wall that obliterates the lumen and spreads centrifugally into surrounding tissues.

Microscopy

– EHEs do not display mature vascular differentiation, a phenotype restricted to the presence of intracytoplasmic lumens containing erythrocytes.
– Tumor cells are arranged in chains and cords of epithelioid cells embedded in a myxohyaline stroma.
– Most EHEs harbor monomorphic nuclei with low grade features.

Immunohistochemistry

– EHEs consistently express vascular markers ERG and CD31 in 20% of cases, but CD34 staining may or may not be present [7].
– EHEs express epithelial markers in 30% of reported cases, including CK7 8, 18 and EMA [8].
– EHEs overexpress CAMTA1 in 90% of reported cases [9, 10].

Ultrastructure

– EHEs do not harbor mature vascular differentiation, but studies with electron microscopy have confirmed the presence of features reminiscent of endothelial cells, including cells with basal lumina, surface-oriented pinocytic vesicles and Weibel-Palade bodies [11].
– Diagnosis can be molecularly confirmed by FISH or RT-PCR identifying the presence of the WWTR1-CAMTA1 fusion.

7.2 Epidemiology and Physiopathology

7.2.1 Epidemiology

In the ConticaBase dataset, among 10,262 new cases of sarcoma, EHEs represent 42 cases (0.4% of all soft tissue/viscera sarcoma) [12]; however, the true incidence of EHE is still unknown. EHE affects patients of all ages, with a median age at

diagnosis of approximately 20–30 years. Both genders are equally affected, and there are no established risk factors for EHE.

7.2.2 *Molecular Pathophysiology*

EHEs are underlined by recurrent t(1;3)(p36;q23–25) chromosomal translocations thought to initiate tumorigenesis. This translocation fuses *WWTR1* (3q23–25) to *CAMTA1* (1p36.23), and the translocation breakpoint may vary [5, 13].*WWTR1* encodes a transcriptional coactivator highly expressed in endothelial cells that has been shown to stimulate differentiation of mesenchymal stem cells [14], and *CAMTA1* encodes a calmodulin-binding transcription factor [5, 14]. Errani et al. have demonstrated that multifocal EHE is a clonal disease, with all tumor foci displaying the same translocation breakpoints [13]. The *WWTR1-CAMTA1* fusion causes translocation of CAMTA1 to the nuclei of tumor cells, leading to constitutive activation of the Hippo pathway [15].

A minor subset of EHEs (approximately 10%) display another translocation (t(11;X)(q13;p11.22)) involving *YAP1* and *TFE3*. However, as opposed to EHE, these *TFE3*-related vascular tumors harbor true vascular differentiation, so it is unclear whether they represent a variant of EHE or a variant of epithelioid hemangioma. YAP1 (11q13) encodes a transcriptional co-activator and similar to WWRT1, YAP1 is part of the FAT-family. TFE3 encodes a microphthalmia transcription factor. EHEs displaying the YAP1-TFE3 fusion gene are diagnosed in young adults and characterized by distinct histological features, including well-formed vascular channels and variably solid architecture [7, 16–18].

7.2.3 *Putative Role of* Bartonella sp.

Bartonella sp. are able to induce vascular proliferation (bacillary angiomatosis, peliosis hepatis., etc.) in immune-depressed or immune-competent humans. Three case reports suggest a relationship between EHE and infection with *Bartonella* sp. In a 13-year boy affected by liver EHE, *Bartonella vinsonii* was found in serial hemocultures, and the pathogen was also found in the tumor [19]. In a 37-year-old woman who underwent hepatic transplantation, *Bartonella* sp. were found in hemocultures performed during a post-operative stay [20]. In a third female patient with hepatic EHE, circulating DNA of *Bertonalla* sp. were observed in hemocultures [20]. However, the morphological features of *Bartonella*-related vascular proliferation are substantially different from the immature vascular differentiation displayed by EHE. Nevertheless, systematic screening for *Bartonella* sp. has not been conducted in EHE since identification of the t(1;3)(p36;q23–25) translocation to test this hypothesis.

7.3 Clinical Presentation, Imaging and Diagnosis

EHE is a very heterogeneous tumor with potential hematogenous spreading, and various clinical presentations exist.

7.3.1 Hepatic EHE (Fig. 7.1a)

Approximately 20% of EHE occurs in the liver. Two-thirds of hepatic EHE occurs in women, and the median age is approximately 45 [21]. Approximately 25% of hepatic EHE patients are asymptomatic at diagnosis. Revealing symptoms are non-specific and include weight loss, fever, fatigue, and jaundice [22–24], with abdominal pain being the most common symptom [21, 23]. Exceptional life-threatening syndromes revealing tumor presence could include Budd-Chiari syndrome, Kasabach-Marritt syndrome (severe thrombopenia due to extensive vascular tumor) or hemorrhagic shock caused by tumor rupture [25, 26]. Approximately 50% of hepatic EHEs are diagnosed at a metastatic stage, exhibiting mostly lung or bone metastasis [21].

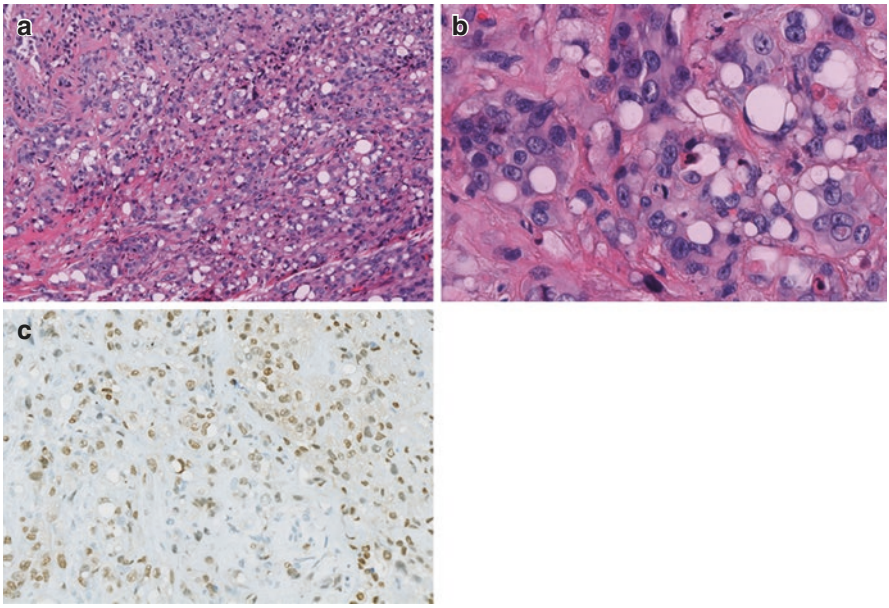

Fig. 7.1 Anatomopathological findings: (**a**) Epithelioid proliferation arranged in solid sheets with focal vacuolization (HES staining, ×150). (**b**) Tumor cells display vesicular nuclei and abundant eosinophilic cytoplasm containing intracytoplasmic vacuoles but no proper vascular lumen. This feature is reminiscent of immature vascular differentiation (HES staining, ×350). (**c**) Immunostaining with CAMTA1 antibody. Positive nuclear staining in tumor cells. CAMTA1 is a surrogate marker of the *WWTR1-CAMTA1* fusion

Imaging of hepatic EHE mainly consists of small retrospective image series with heterogeneous acquisition protocols. Tumors usually appear as mono- or multifocal lobulated peripheral lesions [24]. Calcifications (13–20%) and capsule retractions for subcapsular locations (11–25%) have been reported, as well as a tendency to confluence and to display hypertrophic compensation of the healthy hepatic parenchyma [24, 27, 28].

On ultrasonography, EHEs are classically hypoechogenic [29, 31]. By unenhanced CT-scan, EHEs show low attenuation. After injection with an iodine contrast-agent, enhancement is progressive, rather peripheral and centripetal, with delayed homogenization, which may sometimes lead to misdiagnosis as hemangioma based on this imaging modality alone [29]. However, other patterns can be seen, such as small foci of arterial enhancement, target enhancement, thin or thick ring enhancement or almost no enhancement [30, 32]. On MRI, EHE demonstrate low signal intensity (SI) by T1-weighted imaging (T1-WI) and moderately high, slightly heterogeneous, SI on T2-WI, with a layered 'target-like' appearance [31]. Foci of arterial enhancement, rim-like and then progressive centripetal fill-in may be the most common pattern after Gadolinium chelate injection [32].

Of note, none of these features are specific, and differential diagnoses include atypical hemangioma, metastasis or peripheral cholangiocarcinoma.

7.3.2 Pulmonary EHE (Fig. 7.1b)

Approximately 10% of EHEs occur in the lung. Nearly two-thirds of pulmonary EHE occur in women, with a mean age of 40. In half of cases, pulmonary EHEs are asymptomatic, revealed by imaging performed for other reasons. Revealing symptoms are non-specific and could include fever, weight loss, chest pain (including pleuritic syndrome), hemoptysis or alveolar hemorrhage [33].

Once again, imaging of pleuro-pulmonary EHE relies on small numbers of retrospective studies and case reports. The best modality to investigate this entity is CT scanning.

Three main patterns of EHE tumors have been identified: (1) 'multinodular', made of multiple small (<2 cm) perivascular nodules of which limits can be lobulated, ill or well-defined, with possible calcifications; (2) bilateral multifocal reticulonodular lesions, likely due to combined invasions of vascular and lymphatic structures; (3) diffuse pleural effusion, with moderate enhancement after contrast-agent injection [34, 35]. *According to our studies, PET-CT distinguish various findings, from none to discrete uptake in cases of non-metastatic multinodular pattern, to marked uptake for metastatic EHE with multiple reticulonodular lesions (possibilité de Fig. 7.2).*

Non-(multi)nodular pattern, pleural effusions and hemoptysis are associated with poor outcome [33, 34, 36, 37].

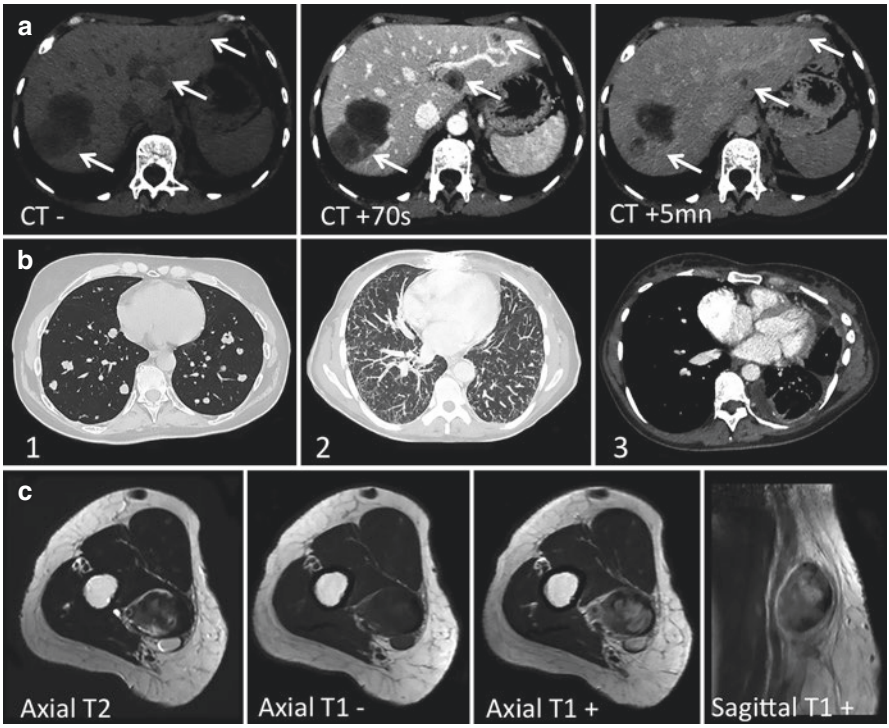

Fig. 7.2 Imaging features of the main locations of EHE. (**a**) Multifocal hepatic EHE including 2 subcapsular leisons (lateral, segment VIII and posterior, segment II-II). The largest one demonstrated low attenuation prior to iodine contrast agent injection (CT-), thick peripheral rim with focal reinforcements on veinous phase (CT + 70 s) and late homogenization, similar to healthy liver parenchyma (CT + 5 mn). Its anterior component remained hypodense, which was compatible with necrosis. (**b**) Pleuropulmonary EHE, showing the three classical patterns on axial CT scan: (1) multinodular pattern (of note, nodules have a tropism for lower lobes); (2) multiple areas of reticulonodular lesions; (3) chronic pleural effusion, with retraction of the left, homolateral hemi-thorax. (**c**) Soft-tissue EHE: MRI demonstrated a deeply-located well-circumbscribed lesion, closely related to the humeral artery with heterogeneous SI on T1-WI, T2-WI after gadolinium-chelates injection

7.3.3 Multifocal EHE

Approximately 20% of EHEs are multifocal at diagnosis, with both liver and lung nodules. Multifocal disease can be asymptomatic. Revealing symptoms could be febrile response with deterioration of general condition, pain, hemolytic anemia and consumption coagulopathy [38].

7.3.4 Soft Tissue EHE (Fig. 7.1c)

Soft tissue EHEs are ubiquitous and appear as a slowly growing, usually asymptomatic, mass of an extremity. They can be superficially or deeply located, with vascular proximity in 50–70% of cases; thus, vascular occlusion is possible. The best

modality to investigate soft-tissue EHE is MRI with gadolinium chelate injection that demonstrates heterogeneous SI on T1-WI, T2-WI and post-contrast T1-WI. Calcifications, spontaneous hemorrhages, peripheral edema and bone erosion may be present [39].

7.3.5 Bone EHE

Bone EMEs are osteolytic, arising from the cortex of medullary bone, with possible cortical disruption and extension into soft tissue. Primary clinical signs consist of pain, swelling, or neurological symptoms in the case of a spine lesion. Bone EHEs are the only location in 14% of cases or can be part of a multifocal disease. Most EHEs occur in long tubular bones of the lower extremities and more rarely in the spine (<10%). Multiple lesions can develop in a single bone or may involve multiple segments with lesions randomly distributed throughout the skeleton or clustered in an anatomic region, such as a single extremity. Tumor calcification can occur, and ultrasonography emphasizes tumor vascularization. CT-scan and MRI patterns are not specific, showing a well-demarcated osteolytic lesion without periosteal reaction in the presence or absence of surrounding soft tissue invasion. Pathologic fractures are possible [40, 41].

7.4 Evolution

EHEs are considered tumors of intermediate malignancy according to the 2013 WHO classification of bone and soft tissue tumors [6]. They follow an unpredictable course, ranging from benign to malignant, as EHE may infiltrate the liver and metastasize.

Risk factors predictive of metastasis have been highlighted and include tumor size over 3 cm with more than 3 mitoses per 50 HPF. The 5-year disease-specific survival is 100% in patients whose tumors lacked these features versus only 59% in tumors with these features [42].

Alternatively, EHEs and multifocal EHEs may exhibit benign behavior over decades. After documentation of disease progression, the median overall survival is approximately 1.3 years. Factors associated with poor outcomes are febrile response with deterioration of general condition, anemia, hemolytic anemia, consumption coagulopathy, and appearance of pleural effusion or ascites [37, 43, 44].

7.5 Management of EHE

Due to the rarity of this disease, there is no consensus regarding clinical management.

7.5.1 Diagnosis

The rarity of EHE and proclivity to mimic other neoplasms make definitive diagnosis difficult. Differential diagnoses require a second opinion by an expert pathologist, as well as confirmatory molecular biology testing for the chromosomal translocation t(1;3)(p36;q23–25).

7.5.2 Extension Check-Up

Thoracic, abdominal and pelvic CT-scan as well as bone scintigraphy could be recommended for assessing disease progression. The role of 18 FDG-PET is not clearly established since the literature contains only very few case reports. Uptake of FDG is inconsistent, and the intensity of uptake is highly variable [45–49]. Before discussing curative surgery, complete check-up is mandatory.

7.5.3 Surgical Approaches

When possible, wedge resection could be considered in unilateral pulmonary EHE. The role of lymph node resection is not clearly established since very few patients present with lymph node involvement [33, 36]. No data are available concerning decortication and resection of pleural tumors.

Localized hepatic EHE could be treated with surgery. Mehrabi et al. report the outcome of eight primary hepatic EHE patients treated with hepatectomy or liver transplantation (five cases). After a median follow-up of 100 months, all patients were alive with three exhibiting recurrence (including in liver for two cases). Recurrence occurred in one out of three hepatectomy patients, and recurrence occurred in two out of five liver transplantations [50]. Thomas et al. report the outcome of seven patients treated with initial hepatectomy. With a median follow up of 51 months, three patients were disease free, three experienced recurrence (one of them died), and one was disease free but died from a different cause. Additionally, no significant difference in overall survival in a series of 50 of hepatic EHEs treated with initial watchfulness (n = 25), surgery (n = 7), or embolization and systemic treatment (n = 18) was observed [21]. Data from literature regarding treatments received by hepatic EHE patients are summarized in Table 7.1.

Bone tumors may require large-en-bloc resection followed by joint reconstruction, preventive stabilization for avoiding pathological fracture, or radiofrequency ablation [40, 51].

Table 7.1 Outcome of hepatic EHE according to treatment

Reference	Study	Treatment	n	5-years OS rate
Mehrabi	Meta-analysis	Liver transplantation	128	55
		Liver resection	27	75
		Syst T/Embolization	60	30
		Observation	28	5
Lerut	Retrospective	Liver transplantation	11	80
Grotz	Retrospective	Liver transplantation	11	73
		Liver resection	11	86
		Syst T/Embolization/Observation	8	29
Wang	Retrospective	Liver resection	17	74
		Syst T/Embolization	13	82
Rodriguez	Retrospective	Liver transplantation	100	64
Thomas	Retrospective	Liver resection	7	83
		Syst T/Embolization	18	71
		Observation	25	72

7.5.4 Radiation Therapy

In bone EHE, radio-induced sarcoma occurs in 8% of patients treated with adjuvant radiation following surgery. Therefore, this treatment should be reserved for lesions not amenable to surgical resection [40]. Few patients (1.2%) with pulmonary EHE received radiation treatment in a large case series (n = 80), resulting in an inability to draw any conclusions [33]. Radiotherapy, despite its potential individual benefit, is not a therapeutic option for hepatic EHE [50, 52], however, radiotherapy can be considered for symptomatic bone tumors.

7.5.5 Initial Watchful Observation

Because some EHEs remain spontaneously stable for decades, a wait and see policy could be considered in cases of slow-growing, asymptomatic tumors not amenable to curative surgery. Furthermore, spontaneous regression of histologically proven EHE has been reported [53–55]. Yousaf et al. reported the outcome of four patients with diffuse EHE managed with initial watchful observation. With a median follow-up of 60 months, only one patient died from the disease 10 years after diagnosis at age 85 [56]. Moreover, Thomas et al. reported the outcome of 25 patients with hepatic EHE managed by initial observation. Among them, disease progression was documented in 14 cases after a median follow-up of 322 days (114–3630). One of these 14 patients died due to rapid disease progression. The remaining 13 patients

either received surgery (n = 2), systemic treatment (n = 8) or local therapies (n = 3), including radiofrequency ablation, embolization or intra-tumoral injection. Therefore, the authors recommend initial watchful observation before considering surgery for EHE in the liver [21].

Despite these findings and recommendations, some presentations suggest an aggressive disease course, including febrile response with deterioration of general condition, hemolytic anemia, consumption coagulopathy and appearance of pleural effusions or ascites. Documented disease progression requires systemic treatment.

7.5.6 Systemic Treatments

There is no consensus on systemic treatment for EHE.

7.5.6.1 Chemotherapy

There are no clinical trials focusing on EHE. By analogy with angiosarcoma (another vascular sarcoma), doxorubicin and paclitaxel have been clinically utilized.

Anthracyclines remain the standard, front-line, systemic treatment for metastatic soft tissue sarcoma; however, anthracycline activity in EHE appears limited. Yousaf et al. found no objective response in six patients treated with liposomal doxorubicin or in two patients treated with doxorubicin [56]. In contrast, two case reports reported partial response with liposomal doxorubicin. Kelly and O'Neil described a patient with aggressive EHE with bony involvement who responded to a liposomal doxorubicin regimen of 45 mg/m^2 every 3 weeks for 20 months, surviving for 24 months from the time of diagnosis with marked deterioration during a break from chemotherapy [57]. Grenader et al. reported a partial response to liposomal doxorubicin lasting more than 18 months in a patient with liver EHE [58].

Yousaf et al. reported on the efficacy of paclitaxel in eight patients. The median duration of treatment was 3 months, without objective response. Nevertheless, despite stable disease, four patients experienced symptomatic benefit, with reduction of analgesia and improvement of performance status [56].

Concerning additional cytotoxic agents, one case report described disease stabilization with gemcitabine lasting 72 months in doxorubicin-ifosfamide-refractory EHE [59]. Another report demonstrated a 90% reduction of pleural EHE after four cycles of carboplatin, pemetrexed and bevacizumab [60]. Yousaf et al. reported one stable disease out of three patients treated with cyclophosphamide in combination with etoposide or vinblastine [56].

7.5.6.2 Interferon Alpha

The Royal Marsden Hospital Sarcoma unit reported the activity of interferon alpha alone in two patients who achieved stable disease (one minor response, with reduction of disease volume of 20%) and the activity of 5FU-interferon alpha combination in three patients, with stable disease as the best response [56].

7.5.6.3 Anti-Angiogenic Agents

The exact role of the VEGF-VEGFR pathway in EHE is unknown. A few studies have shown overexpression of VEGF, VEGFR2 and VEGFR3 in pulmonary EHE [61]. In addition, several anti-angiogenic agents have been used as treatment in EHE, with variable results.

From the reported literature, eight patients have been treated with thalidomide, with the following responses: two partial response, one stable disease and five disease progression [56, 62–66]. Anti-angiogenetic tyrosine kinase inhibitors have also been tested. The EORTC Soft Tissue and Bone Sarcoma Group has reported the outcome of ten patients treated with pazopanib with the following responses: one complete response, one partial response, four stable disease, three progressive disease and one unknown response. Progression-free survival was 26 months [67]. One case report demonstrated a long lasting response (8 years) in a progressive-proven EHE patient treated with pazopanib [68]. The French Sarcoma Group conducted a prospective phase II study assessing the activity of sorafenib in 15 patients with EHE. The median duration of treatment was 124 days and the 2-month, 4-month, and 6-month progression-free rates were 84.6% (11 of 13 patients), 46.4% (six of 13 patients), and 38.4% (five of 13 patients), respectively and two partial responses were observed that lasted 2 months and 9 months [69]. Other case reports are consistent with these results for EHE treatment using sorafenib [70, 71]. Similar results have been observed with sunitinib wherein one patient demonstrated partial response for 22 months and one a stable disease after treatment.

Seven patients with EHE were enrolled in a phase II trial assessing the activity of bevacizumab. Of these patients, two experienced a partial response, while only one patient experience disease progression at first evaluation. The mean number of treatment cycles for this subgroup was 17.3 (52 weeks). Median progression-free survival and median overall survival for these seven patients were 39.1 and 142.6 weeks, respectively [72].

7.5.6.4 Other Agents

Stacchiotti et al. reported activity of the mTOR pathway inhibitor sirolimus. Seventeen patients with EHE received a mean daily dose of 4.5 mg of sirolimus. One achieved partial response, 12 stable disease and three progressive disease as

best response. Median progression free survival was 12 months (1–45), and median overall survival was 16 months [73].

No data exists concerning the therapeutic effect of checkpoint inhibitors or other immunotherapies in EHE patients.

7.6 Pediatric EHE

EHE may occur at any age [23], but childhood cases are extremely rare. Twenty-four cases of pulmonary or hepatic EHE diagnosed under age 18 are described in the literature, with a median age of 12 (4.4–18). Tumor cytogenetics were known in only one case, which did harbor the disease-defining transcript fusion. Outcomes were extremely variable, as was the response to systemic treatment. EHE presented as indolent or aggressive, and similar to adult EHE, children with pleural effusion exhibited worse prognosis, and two patients died within a year from initial diagnosis. Molecular analysis demonstrated a low rate of somatic mutations with no actionable targets, and complete remission was only observed in children who underwent complete surgical resection of the tumor (+/− liver transplantation) [74].

7.7 Therapeutic Strategy

According to recommendations from the literature and due to the rarity of the disease, any suspicion of EHE diagnosis should be confirmed by histological review from a sarcoma reference center. In cases of a resectable disease (unilateral pulmonary nodules, resectable hepatic disease, unique bone lesion), a surgical approach should be the first choice of treatment. In the case of multifocal unresectable EHE, therapeutic decisions should take into account the course of the disease and possible associated symptoms. If a patient appears asymptomatic, an initial “wait and see” strategy could be proposed to evaluate tumor growth rate. Systemic treatment should only be implemented if the patient becomes symptomatic or if tumor growth rate appears significant. If a patient appears symptomatic or presents with life-threatening symptoms (pleural effusion, hemorrhage, etc.), systemic treatment should be initiated without delay. This review of the current literature underlines the paucity of evidence regarding the use of systemic agents for the treatment of EHE patients as well as the lack of independent prognostic factor determination (with the exception of pleural effusion or hemoptysis for pulmonary EHE). Further clinical trials are warranted to determine the best choice of treatment; however, designing new clinical trials is challenging given the rarity of this tumor.

7.8 Perspectives

Tumor collection with post hoc analysis to identify predictive factors for clinical treatment benefit should be performed. However, investigating the best choice for treatment will be challenging. Patients with multifocal EHE should have access to early-phase trials, especially to evaluate efficacy of checkpoint inhibitors and new immunotherapies in this disease. Additionally, patients with unresectable EHE should have access to molecular screening programs in order to prospectively investigate the presence of potential targetable somatic mutations. Currently, only one case of ROS1 fusion in EHE has been described, and such genomic alterations could represent potential therapeutic targets [75], underscoring the importance of identifying further mutations.

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