Rare Sarcomas

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Chapter 1
Clear Cell Sarcoma

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Abbreviations

CCS	Clear cell sarcoma
EFS	Event free survival
HGF	Hepatocyte growth factor
ILP	Isolated limb perfusion
MITF	Microphtalmia-associated transcription factor
OS	Overall survival
PFS	Progression free survival
SLNB	Sentinel lymph node biopsy

1.1 Epidemiology, Clinical Presentation and Prognosis Factors

Clear cell sarcoma (CCS) was first described by Franz Enzinger in 1965 [1]. Since then, only 800 cases have been reported in the literature due to the rarity of this sarcoma accounting for less than 1% of all sarcomas [1–15].

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CCS was also initially called melanoma of soft parts [4] because of its melanocytic differentiation and its clinical behavior which mimics melanoma in some aspects: distal limb distribution, in-transit metastases, regional lymph node spreading and tendency for local recurrence. However CCS remains a soft-tissue sarcoma in other aspects: a deep soft-tissue primary location and a propensity for pulmonary metastases.

In the early 1990s, a specific translocation of this sarcoma subtype resulting in the fusion transcript EWSR1-ATF1 was described, allowing for a better distinction between this tumor and melanomas [16–25]. The nomenclature was thus corrected and the term of CCS has since been retained [4, 8, 9, 15, 26].

This new definition of CCS has resulted in a better selection of cases in published series after the 1990s [9–11, 13, 14], even though confirmation by molecular biology in larger series is low, about 12% or unknown [10, 11]. This molecular biology confirmation is more frequent (60–100%) in recent series which include about 30–50 patients [2, 9, 12–14].

CCS is slightly more common in women than in men in the oldest series and in the series of the MD Anderson [1–4, 27] while many recent series report a majority of men [8–10, 12–14], or an equal distribution [5, 7, 28, 29].

CCS preferentially occurs in adolescents and young adults. The median age at diagnosis is lower than for the other sarcomas, between 26 and 42 years according to the series [2, 7–14, 27, 29], with a global median at 34.7 years (Table 1.1) and a median at 37.2 years for the series with molecular biology confirmation. Cases under the age of 10 years or above 60 years are rare.

The prevalence is higher in Caucasians [2, 7, 29, 30] than in other populations.

The tumor is most often localized on tendons and aponeuroses, predominantly at extremities (in 75–90% of cases) [7, 8, 10, 12–14], preferentially distal. The foot is the first localization, compromising member function [1, 7, 8, 14]. The hip, thigh, knee, and hand are also frequent localizations [5, 30]. Rare localizations have also been described, such as the retroperitoneum, viscera, bone, and the gastro-intestinal tract. The tumor may also develop in the dermis. The epidermis is usually intact whereas the subcutis is then involved in half of the cases. Those primary cutaneous CCS are small (from 0.4 to 1.7 cm) and most of them are located at the extremities [31]. Also, one case of multiorgan involvement was described by Kothaj et al. [32].

In nearly all instances, CCS are thought to arise *de novo* and not from a preexisting benign lesion. Since its first description by Enzinger et al. [1], the hypothesis of a melanocytic differentiation has been retained. Some authors advanced the hypothesis of a synovial [33] or a Schwannian origin [34]. However the most probable hypothesis is a neuroectodermal origin [4, 30, 34–42]. Most cases have no clearly defined etiology, but a number of associated or predisposing factors have been identified, like for other soft-tissue sarcomas, such as family predisposition (germline mutation of p53), toxics (acethyl acids, chlorophenols, dioxin), or immunosuppressive factors (virus, drug). A history of trauma was found in 38% of cases in the study of Enzinger et al. [1] but it might be a coincidence because the preferential localization of CCS are sites prone to injury.

Table 1.1 Published series of CCS: year of publication, inclusion period, number of patients, median age, local recurrence rate, distant recurrence rate, 5 years overall survival, percentage of molecular biology confirmation

Author	Year of publication	Inclusion period	Patient's number	Median age (years)	Local recurrence rate (%)	Distant recurrence rate (%)	5 years OS (%)	Percentage of molecular biology confirmation (%)
Enzinger et al.	1965	1916–1964	21	28	84	63	ND	ND
Chung et al.	1983	ND	141	27	39	50	ND	ND
Eckardt et al.	1983	1925–1980	27	28.5	37	51.8	ND	ND
Pavlidis et al.	1983	1972–1982	6	32	100	83	ND	ND
Sara et al.	1990	ND	17	30	24	64.7	40	ND
Lucas et al.	1992		35	30	14	63	67	ND
Montgomeret al.	1993	1980–1990	58	31	26	44	63	ND
Deenik et al.	1999	1978–1992	30	31	34	60	54	ND
Marquès et al.	2000		36	44	ND	ND	62	ND
Finley et al.	2001	1970–1998	8	33	13	63	55	ND
Kuiper et al.	2003	1985–2002	8	29.5	0	13	ND	12
Jacobs et al.	2004	1980–2002	8	43.4	0	37.5	68	ND
Takahira et al.	2004	1965–1998	14	34.4	ND	ND	33	ND
Kawai et al.	2007	1980–2004	75	36	21.3	69.3	47	9
Malchau et al.	2006	1986–2006	17	34	35.3	52.9	ND	ND
Coindre et al.	2006	ND	44	32	39	43	ND	86
Hisaoka et al.	2008	ND	33	30	7	52	63	100
Clark et al.	2008	1990–2005	72	39	23	63	52	ND
Blazer et al.	2009	1980–2007	52	41	ND	ND	67	54
Stacchiotti et al.	2010		35	45	26	40	ND	ND
Hocar et al.	2012	1979–2005	52	33	56	63	59	54
Ipach et al.	2012	2000–2011	11	47.9	9	100	19	
Bianchi et al.	2014	1976–2010	31	38	26	32	56	64
Total			838	34.7	31	55	54	

The median duration between apparition of the first symptoms and diagnosis is long, about 18 months [8]. Indeed, at the beginning of the disease, this indolent course may lead to a significant delay in diagnosis and treatment. Pain and/or discomfort are present in up to 50% of cases at the time of the diagnosis.

The median tumor size at diagnosis varies between 3 [14] and 5 cm [7] with a majority of 4-cm tumors [9, 10, 12, 13].

The literature data based on retrospective studies agree that CCS is an aggressive disease with a high risk of recurrence and a poor prognosis. Recurrence may occur as soon as 1 month after diagnosis and up to 20 years, with a median time before recurrence of 3 years (38 months) [13]. Particularly, local recurrence occurs in around 20–30% of patients in most series [10, 11, 14, 27, 29], with a fluctuation between 6 and 56% [7, 12, 13]. Time between local recurrence and diagnosis varies between 6 and 33 months. The rate of amputation of the affected limb, around 20% [10, 14] in most series and up to 48% in oldest series [27], is higher than in other sarcomas, probably because of the CCS preferential localization on distal extremities.

Local control is essential because of the high mortality rate reported in case of local recurrence. Indeed, it varies between 60 and 80% [11, 13, 27, 29]. It leaves the surgeon with major difficulties, because he has to grasp the good balance between performing a satisfactory tumor resection and the preservation of the function of the limb.

At diagnosis, the metastatic involvement is about 12% [2, 10] (3–25% according to the series [13, 14, 27]).

Despite local control with surgery, metastases develop in about 60% of the cases (33–70% according to the series), usually 2–4 years after diagnosis, which makes the CCS a disease of poor prognosis [7, 10, 11, 13]. Preferential sites of metastases are lymph nodes and lung, followed by bone and liver [1, 2, 10, 11, 14, 27].

At the metastatic stage, the median overall survival is reported between 7 and 10 months [14, 43]. Overall survival is poor; indeed, all patients died within 24 months [14, 29].

One of the hallmarks of the CCS is its high propensity to metastasize to lymph nodes with a lymph node involvement reported at about 18% at diagnosis, ranging from 12% to 43% according to the series. In other sarcomas, the nodal involvement is much lower, reported in 3–6% of cases [26, 44–46]. A lymph node recurrence occurs in 13–43% of cases according to the series [10, 11, 13, 14].

In the study by Daigeler et al. [47] published in 2009, in 1597 patients with sarcoma, the rate of nodal involvement in CCS was 17.6%. The 1-year and 5-year overall survivals without nodal involvement were 81.5% and 33.3%, respectively, and 55.5% and 12.8% for patients with nodal involvement, thus demonstrating the pejorative impact of nodal involvement. The median time interval between diagnosis and nodal involvement was 4 years, a short interval being correlated with shorter OS ($p < 0.001$).

Nodal involvement is an independent poor prognosis factor, often associated with distant metastasis recurrence, reflecting the aggressive behavior of CCS [45, 47, 48]. However, metastasis occurrence in lymph node only has a pejorative impact

less important on OS than distant metastases occurrence, even for the CCS as reported in the study of Blazer et al. [2, 48, 49].

The overall survival rate at 5 years was reported between 47% and 63%, depending on the series, with a median of 54% [10, 11, 13, 14]. These results are more pejorative than in other sarcomas in which the median 5-year overall survival is around 69% [3]. The high risk of late distant metastasis occurrence induces a very poor prognosis at 10 years, with an overall survival rate at 10 years reported between 25 and 41%, as compared with 60% in other sarcomas.

The most commonly identified poor prognosis factor is the tumor size >5 cm [1, 5–7, 10, 13, 30, 46] followed by the presence of necrosis [1, 6, 7, 13, 50].

The other poor prognosis factors found in the biggest series are the mitotic index >10 [9, 50], presence of metastases at diagnosis [11], local recurrence [27], trunk localization [2, 14], non-Caucasian origin [2], no adjuvant radiotherapy [30], and nodal involvement [10, 27, 30], but most studies lack power due to the small number of patients.

Other poor prognosis factors were found in univariate analysis only: male gender, deep tumor localization and margin invasion [10].

1.2 Specific Localizations

1.2.1 Cutaneous Localization

Few cases of cutaneous CCS were reported in literature. In these cases, a pigmented tumor is localized in the dermis. The challenge is, for these specific localizations, to distinguish these lesions from melanoma lesions. Park et al. described, in 2013, 2 CCS cases: one localized on dermis and the other on subcutaneous fat [51]. For these two cases, CCS diagnosis was confirmed highlighting the specific translocation (EWSR1-ATF1). Cytogenetic analyses of these two tumors revealed unusual mutations in BRAF and Kit, mutations that are rare in CCS but frequent in melanomas [31].

1.2.2 Digestive Localization: In Most Cases a Different Tumor

The digestive localization is rare in CCS. As they show some dissimilarities with their soft parts or cutaneous counterparts, these tumors are named CCS-like tumors of the gastro-intestinal tract. Morphologically, they differ from the soft-tissue CCS: they grow into solid sheets, pseudopapillary or pseudoalveolar formations without well-formed nests. Spindling and macronucleoli are not frequent, whereas necrosis and high mitotic activity are often reported. Half of cases present scattered osteoclast-like giant cells, and tumor cells lack melanocytic differentiation. Electronic microscopy failed to demonstrate the presence of melanosomes in the cases studied [28, 52–54]. The immunophenotype of these

tumors is also slightly different: S100 protein and sox10 are expressed in all cases whereas HMB45, melan A, and MiTF are expressed in significantly fewer cases [55]. Of note, some authors described authentic CCS in the gastro-intestinal tract [55].

For CCS-like tumors of the gastro-intestinal tract, the preferential site is the small intestine (69%), followed by the colon and the stomach [52, 56–58]. The presentation is an ulcerated lesion of the digestive mucosa with a transmural infiltration. The median age is 39 years with a slight feminine predominance and a median tumor size of 5 cm [59]. These tumors are probably under-diagnosed because of the absence of melanocytic differentiation. Molecular tests may be helpful for diagnosis because a specific translocation is found in the form of one of its variants: EWSR1/CREB1 [60]. Other chromosomal abnormalities are described in some series (chromosomes 7, 8, 22). Clinically, these tumors are aggressive with node and distant metastases in 30% of cases. Most of these patients develop liver metastases, or, less frequently, peritoneal metastases. The biggest study on this CCS subtype was published by Stockman et al. [28], and included 16 patients. All tumors were positive for S100 protein and negative for other melanocytic markers. Using FISH, a *EWSR1* rearrangement was found in 85% of cases: among these, 46% were with ATF1 and 23% were with CREB1. The median overall survival was 32 months for these digestive localizations.

1.3 Pediatric Cases

The rarity of CCS in childhood is demonstrated; indeed, only two pediatric series were published, one conducted in the St Jude Children's research Hospital (5 patients treated in 5 years) [61] and more recently, one coordinated by the Italian and German Soft tissue Sarcoma cooperative Group, which included 28 patients treated between 1980 and 2000 [62]. The patients of these two studies represented 0.8% of all pediatric soft-tissue sarcomas registered during the study period.

Clinical characteristics are the same than in adults. The tumor usually occurs in the lower extremities and is intimately bound to tendons, aponeuroses and fascia. At diagnosis, most tumors are smaller than 5 cm diameter. CCS in children have aggressive behavior and tend to metastasize in regional lymph nodes and more frequently in the lung. Nodal dissemination is reported in as many as 50% of cases. Routine nodal sampling or sentinel node lymphadenectomy may then be helpful in staging these patients.

The outcome of pediatric patients seems better than in adults, with a 5-year overall survival rate of 68.9%, and an event-free survival of 62.7% as reported in the series by Ferrari et al [62]. Late recurrence is best reported in the Lucas et al. [6] study in which two-thirds of patients were alive at 5 years after diagnosis but only 33% at 10 years. These data emphasizes the need of long-term follow-up for all patients, both adults and pediatrics. However, in the study reported by Ferrari et al. [62], the median time to recurrence was only 8 months. Predictors of survival are the same

than in adults: tumor size and quality of surgical resection are the most important. Prognosis is also better for pediatric patients whose tumors arise at the extremities compared to tumors localized at other sites. Age, in adults and pediatric patients, did not represent a significant prognostic factor even if pediatric patients older than 10 years showed a tendency for a worse prognosis in the review of the Italian and German Soft Tissue Sarcoma cooperative group [62]. The mainstay of therapy for CCS is adequate surgical resection. In pediatric patients with complete resection, literature data suggest that adjuvant treatment (chemo and radiotherapy) seems unnecessary. Pediatric series are too small to demonstrate any benefit of adjuvant radiotherapy. When conservative complete excision is not feasible, mutilating surgery should be considered. Lymphadenectomy seems to be indicated in case of nodal dissemination. It should be considered for inadequate resections and for tumors larger than 5 cm. Efficacy of the chemotherapy regimens used for other sarcomas and especially rhabdomyosarcoma in advanced or metastatic situation, is not encouraging in children with only one partial response among 9 evaluated patients. Further investigations are needed to define the role of immunotherapy and targeted therapy in CCS pediatric patients.

1.4 Pathology

1.4.1 Macroscopy

The tumor size at diagnosis varies between 0.7 [14] and 25 cm [7] with the majority of tumors around 4 cm [9, 10, 12, 13]. Tumors are mostly round with a smooth or nodular surface, gray to white, and of firm consistency. They are well delineated by a dense fibrous tissue, often firmly attached to an underlying tendon or fascia. Pigmentation and necrosis are rarely seen (Fig. 1.1) [1].

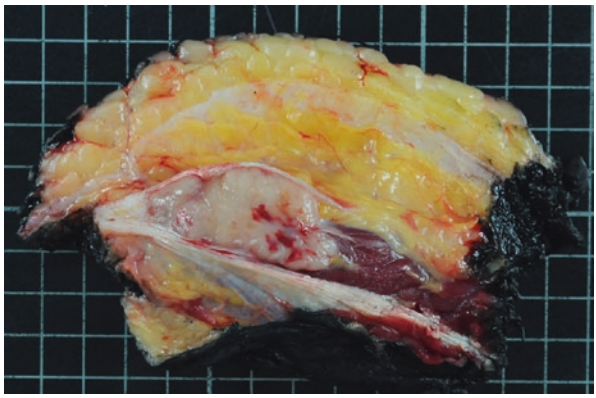

Fig. 1.1 Gross features of a clear cell sarcoma on a resection specimen: fleshy whitish mass arising from a tendon and infiltrating the muscle

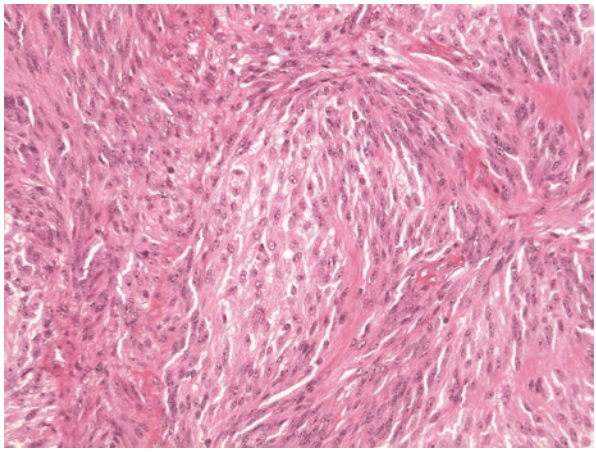

Fig. 1.2 Microscopic features of a clear cell sarcoma (H&E): dense proliferation of large spindled and epithelioid cells, with a prominent central nucleolus. Tumor cells are arranged in short fascicles and nests

1.4.2 Microscopy

Tumor cells are large monotonous polygonal to fusiform cells of epithelioid appearance organized into solid nests and fascicles [1, 4, 9, 63]. Nests are separated by a delicate fibrous framework that merges with the underlying tendon or fascia to which the tumor is attached. Tumor cells have pale (due to glycogen accumulation) amphophilic to eosinophilic cytoplasm with indistinct borders. The nuclei are round to ovoid, small, with finely dispersed chromatin, and with a single large central basophilic nucleolus (macronucleolus). Melanin pigment is only seen in scattered cells at H&E. Fontana melanin stain reveals its presence in about two thirds of cases (Fig. 1.2).

Dispersed multinucleated tumor cells with peripheral nuclei (wreath-like giant cells) might also be seen. They are different from the osteoclast-like giant cells described in the CCS-like tumor of the gastrointestinal tract. Cellular pleomorphism might be seen in recurrences or metastases.

The mitotic activity is usually relatively low, less than 10 mitoses per 10 high-power-fields for half of the cases [10].

The FNCLCC grading system is not applicable to CCS, as they are considered at high risk of metastases.

1.4.3 Immunohistochemistry

CCSs usually show a strong and diffuse staining for S100 protein antibody (up to 100% of cases) (Fig. 1.3). They also show a strong and diffuse staining for melanocytic markers such as HMB45 (in 97% of cases), Melan A (in 71% of cases), and the melanoma isoform of the microphtalmia transcription factor MITF (in 81% of cases) [12, 64], hence the suggestion of Chung and Enzinger to rename CCS, "melanoma of soft parts" [4]. CCS can also express neuro-endocrine and/or nerve

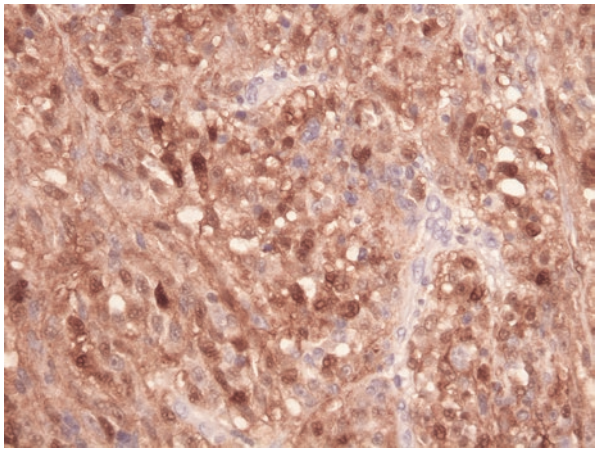

Fig. 1.3 S100 protein immunostaining: heterogenous nuclear and cytoplasmic staining of tumor cells (in brown). Endothelial cells are negative (in blue)

sheath-related markers such as synaptophysin (43% of cases), NSE, CD56, CD57 (75% of cases); they are bcl-2 positive in 93% of cases [12]. Of note, CCS tumor cells may express epithelial markers such as cytokeratins. Apart from the antibodies against the S100 protein and the melanocytic markers, the other listed antibodies above are useless for CCS pathological diagnosis and should not be tested. If needed, molecular testing should be performed.

1.4.4 Molecular Biology

CCS is characterized by a reciprocal translocation (12; 22) (q13; q12) that results in the fusion of the *EWS* and *ATF1* genes, inducing a chimeric *EWSR1/ATF1* gene in which the 3′-terminal part of *EWS* at 22q is replaced by the 3′-terminal part of *ATF1* at 12q [16, 19, 20, 65–67]. *EWSR1* encodes for a RNA-binding protein and is involved in a recurrent translocation associated with a great number of sarcomas: Ewing sarcoma, desmoplastic small round cell tumors, extra-skeletal myxoid chondrosarcoma, angiomatous fibrous histiocytoma, myoepithelial tumor, myxoid liposarcoma, low-grade fibromyxoid sarcoma, …

ATF1 and *CREB1* encode basic leucine zipper transcription factors that are involved in cAMP and Ca^{2+} induced transcriptional activation [68]. The EWSR1/ATF1 fusion transcript is found in more than 90% CCS cases [2, 9, 13, 31], but never found in melanoma, and consists in a diagnostic marker [9].

Four types of EWSR1/ATF1 transcripts have been identified in CCS, designated as type 1–4 [9, 17, 69]. The type 1 transcript (50% of the cases [2]) is an in-frame fusion of exon 8 of *EWS* with exon 4 of *ATF1*. The type 2 transcript (45% of the cases [2]) is an in-frame fusion of *EWS* exon 7 with *ATF1* exon 5, the type 3 (<5% [2]) an in-frame fusion of *EWS* exon 10 with *ATF1* exon 5 and the type 4 (<1% [2]) an out-of-frame fusion of *EWS* exon 7 with *ATF1* exon 7. The presence of multiple transcripts in the same CCS (usually transcripts 1 and 2) has been reported in some

cases [12]. No significant association between the transcript type and the outcome of the patient was found [9].

The EWSR1-ATF1 fusion protein was shown to bind to and activate the MiTF which, in the presence of the Sox10 transcription factor, regulates growth and survival of CCS tumor cells and triggers melanocytic differentiation [70].

Another variant chromosomal translocation t(2; 22) with a *EWS/CREB1* gene fusion was found with little or no melanocytic differentiation, preferentially localized in GI tract [69].

In addition to translocation (12; 22) (q13; q12), polysomy of chromosome 8 was reported as a second abnormality in many CCS cases. Numerical aberrations involving chromosome 22 (other than the t(12;22) translocation) and chromosome 7 are also described in the literature [24, 65, 71].

Contrary to melanoma, the mutations in exons 11 and 15 of the *BRAF* gene were not reported in CSS in the oldest series [17] but *BRAF* mutations were found in others CSS series [13, 51, 72]. Microsatellite instability was shown to be rare or absent [73].

For diagnostic purposes, the EWSR1/ATF1 fusion transcript can be detected by RT-PCR or RNA sequencing from frozen or FFPE tissues. The *EWSR1* gene rearrangement can be detected using FISH (fluorescent *in situ* hybridization) [74].

1.5 Imaging

A wide variety of masses may develop at the limb extremities but malignant soft tissue tumors are rare. The initial imaging evaluation is thus fundamental. It should be performed before the diagnostic biopsy and take place as often as possible in a reference center for the management of soft tissue tumors.

1.5.1 Radiography and Ultrasound

Ultrasonography is usually performed as first-line examination for soft tissue mass evaluation because of its easy access, safety, and low cost. CCS imaging using ultrasound has been poorly described in the literature. Ultrasonography usually shows a well-limited, heterogeneous, echo-enhancing mass, richly vascularized in Doppler.

Radiographs are usually normal; indeed, calcifications in the lesion are rare [30, 75, 76].

1.5.2 MRI

Due to its excellent contrast resolution and multiplanar imaging capacities, magnetic resonance imaging (MRI) has greatly improved the ability to delineate lesions of the soft tissue tumors [75].

On MRI examination, CCS typically have a misleading benign-looking appearance: they are often small and homogeneous, with well-defined borders. The shape is oval, round, or less frequently multilobulated. Intratumoral necrosis is rare (5%). Destruction of an adjacent bone is reported in 10% of cases [77].

On T1-weighted images in a series of 21 CCS cases, half were slightly hyperintense to muscle [77], probably a reflection of the melanin tumoral content [78]. The other cases were hypo or isointense.

On T2-weighted images, the signal was variable, of little diagnostic help. Hypointense foci were correlated with the presence of iron or melanin deposits [75, 79].

More importantly, two thirds of the lesions showed an intermediate or strong enhancement on Gadolinium-enhanced T1-weighted images, suggestive of an aggressive mass.

A close contact to a tendon to an adjacent tendon or fascia was seen in two-thirds of cases [77].

1.5.3 PET-TDM

FDG PET/CT was shown to be a promising imaging modality. However there is no standard in diagnostic indications or follow-up for sarcomas. Fuglø et al. conducted in 2012 a study to evaluate the diagnostic and prognostic value of 18F-FDG PET/CT in the initial assessment of soft tissue sarcoma. They concluded that it has a high sensitivity, specificity and accuracy for the assessment of lymph node and distant metastases. The limit, however, is the low predictive value of a positive test in sarcoma with lymph node metastases [80]. Few cases of CCS show high FDG avidity (SUV = 12.4) [81, 82]. FDG PET/CT might also be helpful in detecting postoperative recurrences of CCS of gastrointestinal origin [83]. The new p-borono-L-phenylananine (BPA) tracer is promising because it plays a role in melanin production and accumulates in melanin-containing cells. As a high accumulation of boron was reported in CCS cell lines, like in melanoma, BPA may be interesting as a predictive factor in clinical use [84].

1.6 Treatments

1.6.1 Surgery

The surgery is the cornerstone of CCS treatment, like in other sarcomas. The challenges of surgical interventions are linked to the periarticular localization of CCS compromising the preservation of limb function and to their indolent phase delaying CCS diagnosis.

The percentage of patients undergoing conservative surgery in CCS is less important than in other sarcomas, 48% in the oldest series [1]. The amputation rate

Table 1.2 Percentage of amputation according to the different studies

Author	Rate of amputation (%)	5 years OS (%)
Enzinger et al.	48	ND
Eckardt et al.	4	ND
Sara et al.	29	40
Lucas et al.	57	67
Montgomery et al.	17	63
Kuiper et al.	0	ND
Kawai et al.	21	47
Hocar et al.	7	59
Ipach et al.	18	19
Bianchi et al.	16	56
Total	21.7	

varies according to the series, between 0% and 57%, with a median about 20% of patients [5, 6, 8, 10, 13, 14, 27, 85], compared with about 1% in other sarcomas [86] (Table 1.2).

1.6.1.1 Sentinel Lymph Node Biopsy

CCS have a high propensity to metastasize to lymph nodes with a lymph node involvement at diagnosis reported in about 18% of patients, ranging from 12% to 43% [35, 46, 47, 87] according to the series. In other sarcomas, nodal involvement is highly less frequent, and varies from 3 to 6% of cases [26, 45, 88].

The positive impact of sentinel lymph node biopsy (SLNB) is widely demonstrated in other tumors in which nodal involvement is frequent, such as melanoma and breast cancer. This technique could be performed in CCS. The study of Al-Refaie et al. was the first to study SLNB feasibility in CCS [89]. SLBN was performed in 3 patients with a success rate of 100% without any aggravation of surgical procedure morbidity. SLNB revealed lymph node involvement in 1 case out of 3. In this study and 2 others, the lymph nodal involvement diagnosed by SLNB was confirmed by lymph node dissection [90, 91]. In other studies on SLNB in CCS, positivity of the SLNB was important: 50% in the study of Andreou et al. [87] and 35% in the meta-analysis of Wright et al. [92]. In the study of Andreou et al., among the 50% SLNB positive patients, about 30% patients had a positive lymph node dissection with unfavorable evolution to death. All other patients had a negative lymph node dissection, and among them, about 75% are still alive at the end of the study with a mean follow-up about 38 months. The impact of SLNB on prognosis was confirmed by the meta-analysis of Wright et al. in which positive SLNB was confirmed to be a poor prognosis factor, regarding local recurrence (22% for positive SLNB patients *versus* 10% for patients with negative SLNB), distant recurrence (57% for positive SLNB patients *versus* 14% patients with negative SLNB) and overall survival (48% for positive SLNB patients *versus* 5% patients with negative SLNB). However, the therapeutic impacts of both SLNB and secondary lymph

node dissection still have to be demonstrated. Given its low morbidity, this procedure could be applied in CCS surgery.

1.6.1.2 Isolated Limb Perfusion

Because of their location at the distal ends of limbs, isolated limb perfusion (ILP) could be a good therapeutic option for CCS. However, in the study of Pennacchioli et al. in 88 patients who underwent ILP, multifocal CCS and epithelioid sarcomas are the histological subtypes for which local disease-free survival at 5 years was the most unfavorable: 40.9% *versus* 67.3% in other histological subtypes ($p < 0.05$) [93].

1.6.2 Radiotherapy

Given the high local recurrence rate and the high amputation rate in CCS, radiotherapy could help surgery improve both local control and conservative surgery rates. No preclinical study has yet evaluated the radio sensitivity of CCS cells. Kinnaert et al. have published in 2000 data showing a decrease in radiosensitivity of melanoma cells, which was inversely proportional to the amount of intracellular melanin [94]. It might be interesting to investigate this point in CCS. Clinical data are rather in favor of a positive impact of radiotherapy in the treatment of CCS. Indeed, in the study by Bianchi et al., three patients who underwent positive margins resection combined with adjuvant radiotherapy showed no local recurrence [14]. In the series of Eckardt et al., the three patients treated with adjuvant radiotherapy had the longest follow-up [27]. Also, in the study of Deenik et al. adjuvant radiotherapy was shown to be a significant good prognosis factor on overall survival [30].

Combining radiotherapy and immunotherapy may be a promising therapy because of the abscopal effect. Indeed, Marcrom et al. described the case of a 26-year old woman with a recurrent mediastinal CCS showing a durable complete response after treatment with radiotherapy (50 Gy) and Pembrolizumab recurrence mediastinal CCS [95].

Preclinical data on CCS cells and mice with lung metastases from CCS showed an antitumoral activity of the Boron neutron capture therapy without damaging the surrounding tissues in comparison with conventional radiotherapy [84, 96, 97].

1.6.3 Chemotherapy

1.6.3.1 (Neo)Adjuvant Chemotherapy

As detailed before, the distant metastasis recurrence rate in CCS is high (55%) (Table 1.1). An effective adjuvant systemic therapy may thus be a good option for patients with CCS. The study of Kawai et al. in 2007 in 75 CCS patients showed a

positive impact of adjuvant chemotherapy in univariate analysis: the overall survival rate at 5 years was 66% in the adjuvant chemotherapy group *versus* 22% in the control group [10]. However, it is the only study that demonstrates the adjuvant chemotherapy interest and its impact on overall survival which was not showed in multivariate analysis. These data and the low response rate to chemotherapy at the metastatic stage should make us reconsider the interest to propose patients with adjuvant chemotherapy.

1.6.3.2 Chemotherapy in the Metastatic Setting

CCS is classically recognized like a chemoresistant tumor. Indeed, in the study by Jones et al. in 24 metastatic CCS patients treated with chemotherapy (anthracyclines ± ifosfamide ± platin), a 4% partial response rate was reported, together with a 58% progression rate. The median progression-free survival was 11 weeks and the median overall survival, 39 weeks. For patients treated in second-line, the progression rate was 92% and in third-line, it dropped to 80%. In the study by Hocar et al., 24 patients were treated with chemotherapy for their metastatic disease. No efficiency was reported in 21 patients, most of the time after the first 3 cures [13]. The study by Kawai et al. showed a best partial response rate of about 23.3% for patients treated with chemotherapy based on cisplatin [10]. In addition to this study, few cases report a good response to the following chemotherapy regimens, Dacarbazin/Vincristin/alkylating agent, or Bleomycin/Vincristin.

Caffeine was used in association with chemotherapy in CCS in 2 studies. Takeuchi et al. showed that a combination of cisplatin, doxorubicin and caffeine had an objective response rate in 80% of CCS patients [98]. This was confirmed by Karita et al. who demonstrated in 4 metastatic CCS patients 2 complete response and 2 partial response after treatment with chemotherapy by doxorubicin, cisplatin and caffeine in intra-arterial before surgery and intravenous after surgery [99]. The mechanism of an antitumoral effect of caffeine is not known yet. However, caffeine was shown to have a synergic antitumoral effect when given in combination with chemotherapy. To explain this observations, the main hypothesis is that caffeine may potentiate chemotherapy by inhibiting DNA repair [43, 100, 101].

1.6.4 Targeted Therapy

1.6.4.1 VEGR and PDGR Inhibitors

In a large proportion of CCS expression and activation of PDGFRB is found [72, 102]. CCS share with alveolar sarcoma some characteristics: they are translocation specific sarcoma, they belong to the MITF family and tumor cells express PDGFRB.

The Sunitinib (VEGFR, PDGFRA/B, Kit, FLT3, RET, M-CSFR inhibitor) was assessed in alveolar sarcoma by Stacchiotti et al. with encouraging results with

median PFS at 17 months [103]. They tried the Sunitinib on CCS because of the common features with alveolar sarcoma on one patient with a response objective beyond 3 months [104]. Another report case showed a partial response with Sunitinib in pretreated CCS patient with stabilization of the disease during 12 months [102].

One case of response to Sorafenib (VEGFR2-3, PDGFRB, Kit, BRAF inhibitor) is described with a stabilization of the disease during 8.2 months [105].

One case of stabilization during 23.6 weeks in pediatric metastatic CCS patient with Aflibercept (VEGF-A and B inhibitor)

Cediranib (VEGF inhibitor) was assessed in phase III versus placebo in alveolar sarcoma with good results: decrease in tumor volume, increase objective response and improve overall survival at 1 year (96% versus 64.3%), demonstrating that a phase III can be performed on such a rare tumor (Judson et al. abstract 11004 ASCO 2017).

For the Pazopanib in CCS, we only have preclinical data available that showed that Pazopanib inhibits cMET in vitro and in vivo via autophosphorylation inhibition which results in delaying tumor growth by stopping the cell cycle [106].

1.6.4.2 MET Inhibitors

CCS is characterized by the specific translocation t(12:22) responsible for producing a fusion transcript that leads to the activation of MITF (Microphtalmia-associated transcription factor) that increases the transcription of *c-MET*.

C-Met is a pro-oncogene frequently dysregulated in cancers. Its ligand is the HGF (Hepatocyte Growth Factor) which is expressed by stromal and mesenchymal cells. By its ligand fixation or autophosphorylation of its tyrosine kinase domain c-MET stimulates the cells proliferation, the cells survival, the invasion, adhesion, and migration. Apart from increasing c-MET transcription, MITF is also implicated in regulation of p16 (cell cycle regulation) and Bcl2 (cellular survival).

The excessive expression of MET and the Pi3K/Akt way and ERK way activation ensuing was demonstrated preclinically on CCS [70, 72] as well as the aberrant expression of MITF.

MITF tumors associated are a family of rare tumors including CCS, alveolar sarcomas, and the renal carcinomas linked to the Xp11.2 translocation. Although morphologically and clinically different these tumors share common characteristics: high incidence in young patients, chemoresistance, high metastatic potential.

Preclinical studies were encouraging, Davis et al. showed that in CCS, c-MET was expressed in autocrine-activated manner (by HGF). The c-MET activity blockage by ITK (SU11274) or by an antibody directed against its ligand HGF (AMG102) reduced significantly CCS cells growth. The impact on tumor growth was observed also on xenograft for the antibody AMG102 [70, 107].

However the results of clinical studies are disappointing, the phase II evaluating the effect of Tivantinib (a selective c-MET inhibitor) showed in CCS 9% of partial response, 27% of stable disease with a median PFS at 2.8 months. The explanation could be that there are other key factors implicated in proliferation and cell survival in CCS like EGFR (Epidermal Growth Factor) way [108]. The results are better for

Crizotinib (c-MET, ALK and ROS inhibitor): on 28 CCS screened, 26 were included (MET+) with 69.2% of objective response, median PFS of 4.4 months and median OS of 9.2 months. These results are the same than the results with pazopanib in pretreated soft tissue sarcoma patients [109].

1.6.4.3 Immunotherapy

The common features between CCS and melanoma leads us to ask the question of immunotherapy interest in CCS. 2 cases of metastatic CCS with a durable response of 17 months to Interferon delivered in intralesional or intravenous in combination with chemotherapy [110, 111]. In the study of Merchant et al. 2 pediatric metastatic CCS patients were treated by Iplilimumab (CTLA-4 inhibitor) with a stabilization for disease during 6–24 months [112]. With the Pembrolizumab one partial response and one complete response in metastatic CCS patient were reported [95, 113].

1.6.4.4 Others

BRAF Inhibitors

There are some cases of *BRAF* mutations in CCS in the literature: 3.8–23.8% according the series [13, 51, 72]. In these cases of *BRAF* mutation some major responses has been published like Protsenko et al. who described a complete response of metastatic CCS patient with *BRAF* mutation to Vemurafenib [114].

HDAC Inhibitors

Preclinical data on HDAC inhibitors are interesting; indeed CCS cells are sensitive to HDAC inhibitors in vitro by inducing histone H3 acetylation thus creating a stop in the cell cycle, apoptosis, and differentiation induction. HDAC inhibitors inhibit fusion transcript expression [115].

Her3 Pathway

Her3, a member of EGFR receptor, is overexpressed in CCS [72, 116, 117] with in all the cell lines a co-expression with Her2 and/or Her4, there is an overexpression of neuregulin-1 (an activator of Her3) in only half of cell lines. 2 pan-ERB tyrosine kinase inhibitors were used with an inhibition of CCS growth correlated with neuregulin expression indicating a possible autocrine growth stimulation loop which could be a new target.

1.7 Conclusion

Clear cell sarcoma of the tendons and aponeuroses is an aggressive, rare soft-tissue tumor, with a propensity for lymph node metastases and characterized by multiple local recurrences with late metastases and a high rate of tumor deaths. The FNCLCC grading system is not applicable to CCS, as they are considered at high risk of metastases. Surgical treatment may be beneficial for tumor without systemic involvement. Nodal involvement is frequent and is an independent poor prognosis factor, often associated with distant metastasis recurrence. The sentinel node procedure might be a useful and accurate staging procedure in clear cell sarcoma patients. Systemic treatment options are poorly standardized and the use of chemotherapy is based on weak scientific evidence. In a large proportion of clear cell sarcoma, expression and activation of PDGFRB has been found and objective tumor responses observed upon tyrosine kinase inhibitors. A phase 2 trial is recruiting to determine the efficacy of cabozantinib in patients with recurrent or refractory CCS (NCT02867592). A recent phase II trial demonstrated that crizotinib (MET inhibitor) provided a clinical benefit in almost two-thirds of cases. The common features between CCS and melanoma lead us to ask the question of immunotherapy interest in CCS, supported by the publication of several clinical case reports with objective responses.

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Chapter 2
Epithelioid Sarcoma

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2.1 Definition and Bio-Pathologic Diagnosis

2.1.1 Definition

Epithelioid sarcoma (ES) is a rare subtype of soft tissue sarcoma (less than 1% of soft-tissue sarcomas). The first description was in 1970 by Enzinger [1], after being described as aponeurotic sarcoma by Laskowski in 1961 and like "a large cell sarcoma of tendon sheath" by Bliss and Reed in 1968. It is presumed to be a mesenchymal malignancy as they develop primarily in soft tissue, although ES exhibit both mesenchymal and epithelial markers.

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2.1.2 *Criteria for Diagnosis*

Macroscopy
Macroscopic findings are poorly specific. ES present as solid, multinodular mass, with infiltrating margins, gray or white-tan appearance. Tumor size range from 15 to 150 mm, with a mean of 36 mm [2]. Areas of necrosis and hemorrhage are common, in line with the high grade features of these tumors [2–5].

Microscopy
Histologically, two morphologically distinct subtypes of ES have been delineated, correlating with their distinct clinical presentations. First, ES distal type present with pseudo-granulomatous nodules, infiltrating superficial tissues, commonly complicated with skin ulceration. In this subtype, tumor cells are more heterogeneous displaying epithelioid to spindled appearance. Tumor cells are intermingled with inflammatory infiltrate containing histiocytes, polynuclear cells and lymphocytes which may overshadow tumor cells. Second, ES proximal type display a more straightforward appearance composed of epithelioid tumor cells arranged in sheets. ES, proximal type typically display large areas of necrosis and hemorrhage [6] (Fig. 2.1). Tumor cells display large vesicular nuclei atypical but not pleomorphic and abundant eosinophilic cytoplasm (Fig. 2.1). Rhabdoid features may be focally present defined as eosinophilic paranuclear condensation [6]. ES are not graded but considered as high grade tumors [7, 8].

Immunohistochemical Features
ES display diffuse keratin expression, an unusual feature in mesenchymal tumor [1], including wide or low spectrum keratins and epithelial membrane antigen. CD 34 is positive in half of ES [9, 10]. By definition, all ES lose SMARCB1/INI1

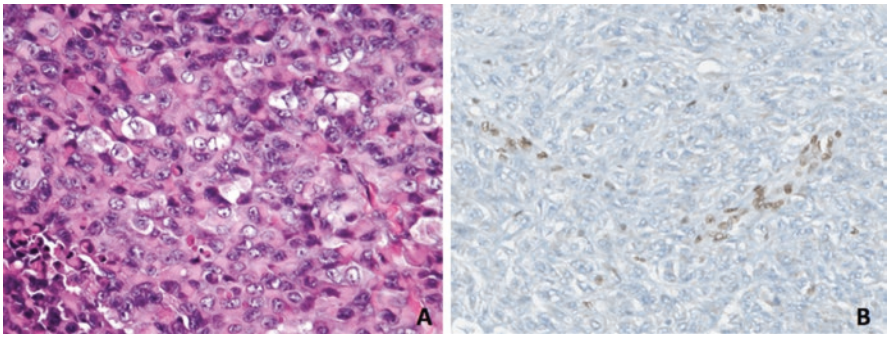

Fig. 2.1 (**a**) ES, proximal type composed of sheets of epithelioid cells with abundant cytoplasm and large vesicular nuclei. (**b**) Immunostaining with SMARCB1/INI1 antibody showing loss of normal nuclear expression of the protein in tumor cells while normal endothelial and inflammatory cells retain normal expression of INI1/SMARCB1

expression [10]. The few SMARCB1-retained cases reported in the literature presumably represent misdiagnosis [11, 12]. ES are notably negative for ERG staining [10] and for SALL4 [13].

Molecular Features

Their underlying molecular features have long been controversial with initial cytogenetic reports of chromosomal abnormalities in the 22q region within *SMARCB1/INI1* locus [14].

Bacterial artificial chromosome-comparative genomic hybridization (BAC-CGH) studies reported occasional *SMARCB1* genomic deletion in ES [15] while mutations were exceedingly rare [16, 17]. Recent studies performed on homogeneous series of epithelioid sarcomas with array-CGH and multiplex ligation probe amplification (MLPA) evidenced that virtually all ES are underlined by 22q11 deletions variable in size but always encompassing *SMARCB1* locus [11, 12] (Fig. 2.1). Interestingly, *SMARCB1* is a potent tumor-suppressor gene involved in the tumorigenesis of malignant rhabdoid tumors (MRT) [18]. MRT predominantly affect infants and children although it may occur at any age [19]. In MRT, *SMARCB1* inactivation occur mainly through loss of function mutations [19]. This gene encodes for a key subunit of SWI/SNF chromatin remodeling complexes in charge of gene translation regulation [20]. The frequency of loss of SMARCB1 expression is the same in primary tumors, local recurrences and metastases, suggesting that this mutation occurs early in the tumor genesis [9].

A relation between ES (proximal type especially) and MRT has long been suspected based on their overlapping morphological features and the involvement of the very same tumor suppressor gene. ES occur primarily in young and middle-aged adults as opposed to MRT which predominate in children. ES have not been reported so far in patients with rhabdoid tumor familial predisposition syndrome. However, a patient affected by ES distal type have been shown to carry SMARCB1 heterozygous deletion in normal tissue but the clinical significance of this isolated report remain unknown [12]. MRT are extremely aggressive and nearly always rapidly fatal while ES, display a protracted clinical course. This loss of expression is also describe in many tumors like rhabdoid tumors, epithelioid malignant schwannomas but not in metastatic carcinomas, melanomas, epithelioid angiosarcomas, histiocytic sarcoma which are also differential diagnosis of ES [10]. In comparison with rhabdoid tumour (the other major group of INI1-negative cancers), epithelioid sarcoma shows a relatively high level of genomic aberrations [21]. Although, all cases are characterized by loss of INI1 expression, more than 30% of them have no genetic aberration of INI1 [21]. The mechanism of INI1 protein loss in this INI1-wild type epithelioid sarcoma is not fully understood and may involve epigenetic events such as methylation.

CA-125, a serum antigen commonly used as a marker for ovarian cancer, was recently shown to be over- expressed in ES tumors (between 76 to 91%) [22, 23]. Kato et al. concluded that CA125 can be a very useful marker in the differential diagnosis of ES from other mesenchymal soft tissue tumors.

2.2 Differential Diagnosis

ES distal type may be histologically confused with benign/reactive granulomatous reaction as the inflammation may obscure tumor cells. Conversely pseudomyogenic hemangioendothelioma may be misdiagnosed as ES due to expression of CD34. However they do not lose SMARCB1 expression and express specific vascular markers such as ERG. ES, proximal type may pose diagnostic difficulties with malignant rhabdoid tumors. The expression of the embryonal marker SALL4 favor the diagnosis of rhabdoid tumor [13]. The consistent expression of cytokeratins may also mislead to a diagnosis of carcinoma [24].

2.3 Epidemiology and Physiopathology

2.3.1 Epidemiology

ES represent less than 1% of soft-tissue sarcomas (0.03%) [25]. It is more common proportionally in young patients, accounting for about 2% of pediatric soft-tissue sarcomas. All of recent studies have a very similar description of Chase and Enzinger in 1985.

More than 75% of patients have an age between 10 and 39 years [2], the mean age is around 30 years [2, 5, 26]. There is a male predominant with an index of 1.8–2.7 men for 1 woman [2, 5].

Distal limb locations are most common, especially the distal upper limb (up to 58%) [1, 2, 4, 26]. Next in frequency are distal lower limb (15%), proximal lower limb (12%), proximal upper limb (10%), trunk especially penile and vulva (3%), head and neck (1%) [2] (Fig. 2.2).

The classic subtype is reported nearly twice as often as a second the proximal subtype [8].

2.3.2 Physiopathology

The histological origin of ES remains unknown and still a matter of debate. No murine model has been developped to apprehend their pathogenesis.

2.4 Clinical Presentations

The tumor frequently appears as a firm nodule, often accompanied by ulceration, hemorrhage and necrosis plaques (Fig. 2.3). The lesion grows slowly, can invade dermis, subcutis and depth in soft tissue, the margins are often raised. Size can

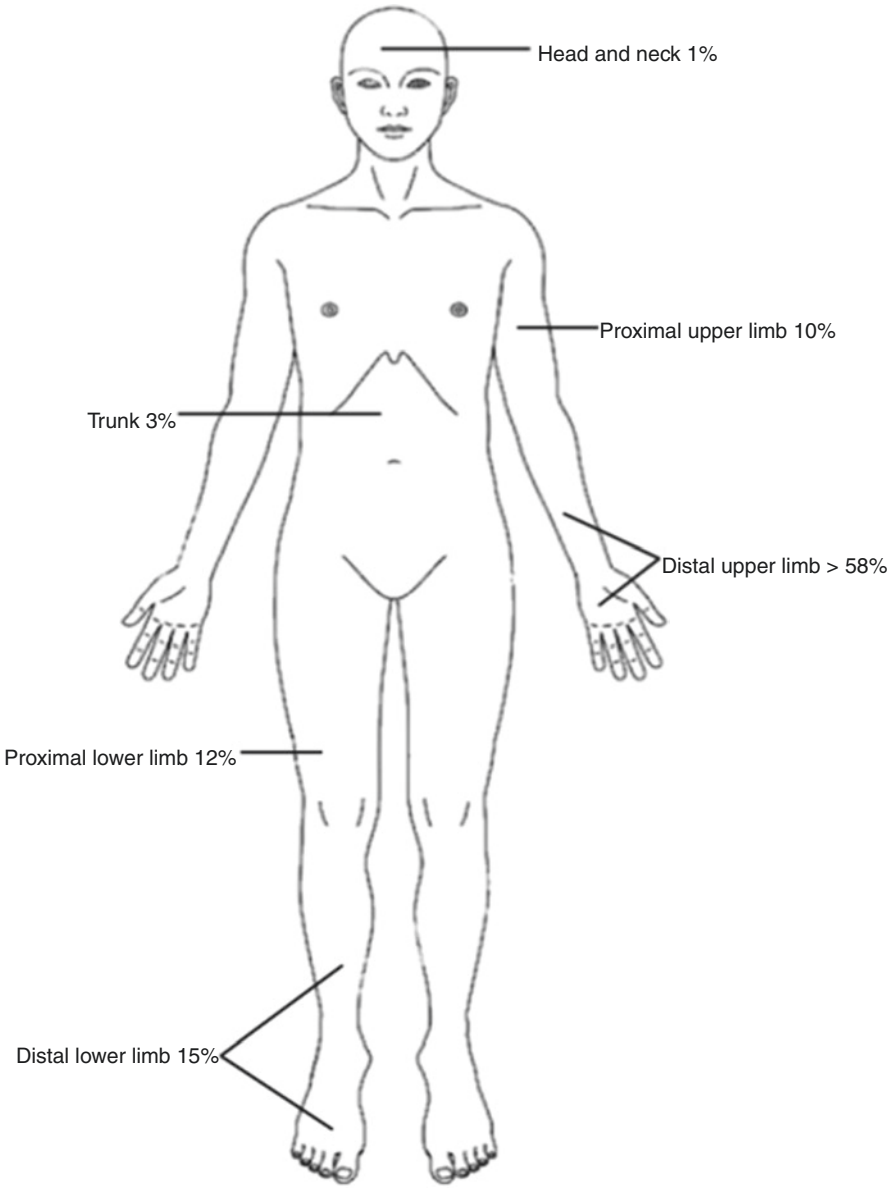

Fig. 2.2 Anatomical distribution of ES

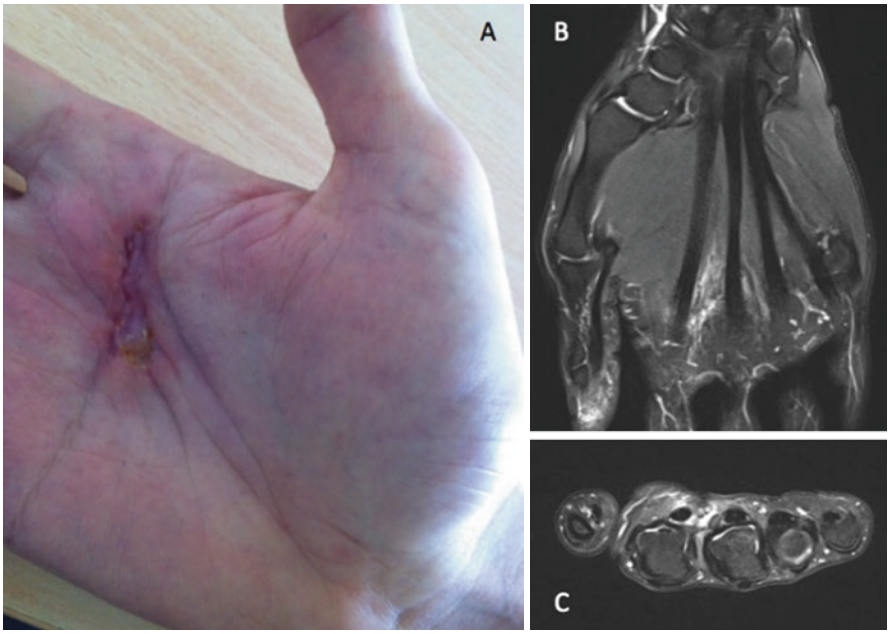

Fig. 2.3 (**a**) man aged 18 years, for several months evolution of an ulcerated mass of 6 cm on the palmar face of the right hand. (**b–c**) MRI: poorly limited lesion, burrowing and infiltrating. 39 × 19 × 15 mm. Subcutaneous lesion that extend deep to the fascia, and to the muscles. T1 hypointense (**b**), T2 fat hypersignal with enhancement after gadolinium injection (**c**)

attain 200 mm in diameter. Pain and sensitivo-motor disorders are variable depending on the location. It can extend along tendon sheaths, facial planes and aponevroses [2].

Many cases (up to 27%) [2, 27] has been associated with antecedent of trauma (crush injuries, bone fractures, scar tissue, site of tattoo...) but no causal relationship is demonstrated.

2.5 Evolution

ES has a local recurrence rate up to 70% in some series [2, 26], it's very important unlike other soft tissue sarcomas. Median time interval from surgery to first local relapse for those who relapsed is 9–10 months [5, 26]. ES has a tendency to spread locally, probably by way of lymphatics or along fascial planes, and regional recurrences are nodes or transit-type metastases. The rate of occurrence of lymph node metastases in ES is between 22% and 45% [4, 5, 26]. This rate is considerable compare with the rate of 2.6% for all subtypes of soft tissue sarcoma combined [28]. The mean length of time to the development of nodal recurrence from local excision is 18 months [26].

In regard to distant metastasis, the most common site for ES is pulmonary, like other soft tissue sarcomas with rate from 21 to 44% [2, 5, 26]. The 5-years distant metastasis rate is 40–45% [1, 5, 26]. The other sites of metastasis disease are: scalp (from 8 to 22%) and rarely in other soft tissues, bones, brain [1, 5].

The overall survival at 5- and 10 years for all ES is between 45–80% and 42–62% respectively [2, 4, 5, 8, 26, 29]. Median survival for all stage is around 80–90 months from the time of definitive diagnosis. The median survival after diagnosis of distant metastases is between 5 and 28 months [5, 26, 30].

Adverse prognostic factors in both classic and proximal subtype are hardly specific, including : older age, male sex [2, 26], the size of the primary lesion, especially more than 5 cm [4, 31], multifocality [2, 4, 5], the depth of the tumor (in relation to deep fascia) [5, 29], mitotic activity, extensive necrosis, proximal limb tumor [1, 2], locoregional and metastasis disease [5], lymph node involvement and R1 resection [4, 5]. ES, proximal type display a more aggressive course which is most probably related to their deep-seated location delaying their diagnosis [6, 32]. The rate of local recurrence (65%), of metastasis (40–75%) are higher, and earlier [7]. But it is not certain if the reduced survival associated with the proximal subtype is due to its different histomorphology or to its lesser surgical resectability because of the deeper location.

2.6 Management of ES [6]

There is no consensual guideline, the literature is essentially composed of case report or small series of ES or in large series of STS with some cases of ES. Accordingly, the therapeutic approach for ES reflect the standard to high grade STS [33, 34].

In childhood and adolescence, pediatric oncologists consider ES among the large and heterogeneous group of non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) that differ from rhabdomyosarcoma (RMS) by their relative insensitivity to chemotherapy and radiotherapy.

2.6.1 Diagnosis and Staging Procedures

MRI is the main imaging modality for STS of extremities (Fig. 2.3). The standard approach to diagnosis consists of multiple core needle biopsies (>14 to 16 G needles) preferably after multidisciplinary discussion with a reference center. The biopsy should be achieved by a radiologist or a surgeon, ideally in a reference center and by the surgeon who will operate the patient, because it must be planned in such a way that the biopsy pathway and the scar can be removed by definitive surgery [33].

Histological diagnosis should be made according to the 2013 WHO classification. All cases have to be confirmed by a pathological expert validation if the original diagnosis was made outside a reference center [33, 35].

A chest CT scan is mandatory for staging, to diagnose pulmonary lesions, the main site of metastasis. Because of a high rate of occurrence of lymph node metastases in ES, regional assessment through CT scan or MRI may be added [33]. Asano et al. perform PET-CT examinations to evaluate lymph node involvement. If it is suspected they planned a lymph node dissection [36].

2.6.2 Surgical Approaches

Surgical excision remains the primary modality of treatment for the patients with ES. It must be performed by a surgeon specifically trained in the treatment of sarcoma [33]. The standard surgical procedure is a wide excision with negative margins (R0) and without tumor rupture. Cut-off the minimal margin may depend on several factors, including subtype, preoperative therapies and presence of anatomical barriers such as fascia.

Several reports have clearly shown that amputation for STS, although decreasing local recurrence, does not lead to improved survival [37]. Rosenberg et al. concluded in a randomized trial, that there is no difference in disease-free survival and overall survival rates between the limb-sparing resection with radiotherapy and amputation in the STS of extremities [38]. This is also observed in ES, despite the highest rate of local recurrence than other sarcomas [39]. Amputation seems to be reserved for tumors not otherwise adequately resectable.

If the resection is R1, reexcision in reference centers must be considered if adequate margins can be achieved without major morbidity. In the case of R2 surgery, reexcision in reference centers is also mandatory.

If adequate margins cannot be achieved or surgery is mutilating, preoperative treatments can be discussed [33].

Surgery of regional lymph nodes in STS is not recommended if there is no radiological argument for tumor invasion. Nevertheless in ES the rate of regional lymph nodes is much higher than the other STS. Wolf et al., suggested a benefit to aggressive surgical excision of nodal disease so they raised a role for sentinel node biopsy [40]. Maduekwe et al. studied the role of sentinel lymph node biopsy (SLNB) in ten cases of non-metastatic ES: a positive SLNB does not necessarily imply development of future metastatic disease and a negative SLNB does not necessarily imply a good prognosis. Additional, it is unknown if earlier identification of occult lymph node metastases using SLNB followed by lymphadenectomy would result in improved survival compared with lymphadenectomy for lymph node metastases found by physical examination or radiological imaging [41].

2.6.3 Radiation Therapy

General indications for postoperative radiotherapy (RT) in wide excision of STS are: high grade and large tumors >5 cm located deep to the fascia. In R1–R2 excisions, radiotherapy is indicated when re-excision is not possible [33, 42]. Studies confirmed that postoperative RT for STS of the extremities provides a good control disease in long term [38, 42]. For ES, data come from studies with very few patients and found an improvement of local control but not significant for OS [40, 43]. RT dose is 50 Gy in 1.8–2 Gy fractions, possibly with a boost to 66 Gy, depending on localization and resection margins.

RT can also be consider when surgery is not possible or refused by the patient. Symptomatic locations (pain, bleeding, compression) can be treated by RT. In some cases of oligo-metastatic disease, it may be discussed ablative treatment (particularly pulmonary metastases) by RT.

2.6.4 Isolated Limb Perfusion (ILP)

ILP with or without TNF-α + melphalan may provide a limb salvage option for locally advanced STS not amenable to local resection [33, 44, 45]. Levy et al. confirm this role of limb salvage in locally advanced or multifocal ES. 77% had an objective response (24% RC, 53% PR) and a local control relatively similar than data literature in patients treated with conservative management. This study also confirm that amputation did not improve OS and multimodal management must be proposed to avoid amputation [46].

2.6.5 Systemic Treatments

Preclinical data showed that EZH2 inhibition leads to specific repression of cellular H3K27 methylation and induces apoptotic death of INI1-negative malignant rhabdoid tumor cells [8, 9]. These findings suggest a synthetic–lethal interaction between INI1 and EZH2 and consequently offer a promising therapeutic approach in INI1-negative tumors. Tazemetostat (EPZ-6438) is a potent and highly selective EZH2 inhibitor [9, 10] that has shown activity in INI1-negative MRT cells, both in culture and in xenograft experiments in vivo. In 2013, a phase 1 trial was initiated to evaluate the safety and toxicity profile of daily oral administration of tazemetostat in patients with metastatic or locally advanced solid tumors or non-Hodgkin lymphoma (NHL) (NCT01897571) [47]. In June 2014, the team of Pr Antoine Italiano (Institut Bergonié, Bordeaux, France) enrolled in this study the

first patient with INI1-negative solid tumor. This patient who suffered from a relapsed MRT displayed a complete response which lasted for more than 4 years. This event prompted enrolment of additional patients with these genetic lesions to more fully evaluate the activity and safety of the drug in this population. The investigators observed clinical activity consisting of objective responses (complete responses and partial responses) or prolonged stable disease (6.4 to >20 months), which has exceeded a duration of 2 years in five (38%) of 13 patients with INI1-negative or SMARCA4-negative solid tumours [47]. Interestingly, none of the patients with tumours bearing wild-type expression of INI1 or SMARCA4 proteins had an objective response. Tazemetostat was well tolerated, with most treatment-related adverse events being grade 1 or 2 (asthenia, anorexia, thrombocytopenia, nausea and dyspnea). These encouraging preliminary results led to the design of a basket phase 2 study investigating tazemetostat in INI1-negative tumors (NCT02601950). With only 2 objective response among 31 patients, stage 2 futility was not passed in the rhabdoid tumor cohort [48]. The results obtained in the epithelioid sarcoma cohort are more promising and potentially practice-changing [49]. Existing cytotoxic drugs (including doxorubicin) are associated with modest efficacy in patients with advanced epithelioid sarcoma. Sixty-two patients (24 in the 1st line setting and 38 who already received systemic therapy) were enrolled in the tazemetostat study [49]. At data-cutoff, the overall response rate was 15% [9/62, 95% CI, 6.9 – 25.8] (25% for patients in the 1st line setting and 8% for those who had prior systemic therapies). At a median follow-up of 59.9 weeks, the median duration of response was not reached. The overall disease control rate (partial response or stable disease ≥ 32 weeks) was 26% (95% CI 15.5 – 38.5). The median progression-free survival was 23.7 weeks (95% CI, 14.7 – 25.7) and median overall survival was 82.4 weeks (95% CI, 47.4 – NE). As observed in the phase I study, the safety profile of tazemetostat was good and compared favourably with that of commonly used cytotoxic drugs such as doxorubicin and gemcitabine. Altogether, these results showed that tazemetostat can be associated with substantial clinical benefit in a subset of patients with advanced epithelioid sarcoma. Based on these data, the United States Food and Drug Administration (USFDA) granted accelerated approval to tazemetostat for the treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection in January 2020. Therefore, tazemetostat (TazverikTM) is the first epigenetic drug approved for the treatment of patients with solid tumors. However, several questions regarding the role of tazemetostat in the treatment of patients with epithelioid sarcoma will require further investigations.

Preliminary data have suggested that DNA methylation profile may correlate with outcome of patients on tazemetostat but require further confirmation before this can be considered as a potential predictive biomarker [21]. Finally, the excellent safety profile of tazemetostat may allow potential combination with other agents. Combination with cytotoxic drugs may represent a promising approach as suggested by pre-clinical data showing synergy between tazemetostat and doxorubicin [50.]. A phase Ib investigating the safety of tazemetostat in combination with doxo-

rubicin is ongoing (NCT04204941) and a phase III that will compare doxorubicin versus doxorubicin combined with tazemetostat in the front-line setting for epithelioid sarcoma treatment is planned to open accrual in 2020. In addition to cytotoxic drugs, immune-checkpoint inhibitors (ICI) can represent another interesting class of agents to combine with tazemetostat. Italiano et al. have reported a strong induction of CD8 T cells in a patient with epithelioid sarcoma treated with tazemetostat [47]. This immune infiltrate was neither present at baseline nor in a later specimen collected at disease progression. Several studies have shown a role of EZH2 in immunomodulation [51]. Together with the recent demonstration that EZH2 inhibition enhances ICI efficacy in pre-clinical models of melanoma and other solid tumors [52, 53]. Clin Cancer Res. 2019;10.1158/1078-0432.], these findings pave the way for clinical trials combining ICI with tazemetostat in epithelioid sarcoma and other INI1-negative solid tumors.

2.6.5.1 Chemotherapy

About adjuvant chemotherapy after sarcoma resection, there is no a consensus [33]. A specific review from the Cochrane Database found a statistically significant benefit in term of local recurrence-free interval, distant recurrence-free interval and overall recurrence-free survival, but the OS was not significant. Even if the strongest evidence of a beneficial effect on survival was shown with sarcoma of the extremities [54], interest seems modest in ES given the low rate of response to chemotherapy.

In the metastatic or locally advanced setting, the first-line treatment, like the STS, is chemotherapy based on anthracyclines. Multi agent chemotherapy is not superior to single agent with doxorubicin alone in terms of overall survival. Some studies have analyzed the role of palliative chemotherapy in advanced ES specifically. All are retrospective studies. The largest recent series confirms the activity of anthracyclines-based regimen in 72 ES, with a response rate (RR) of 25% and a 6 months PFS [55]. 2 studies reported activity of adriamycine more and less ifosfamide. Jones et al. observed 20 patients in the first line, they described 15% of partial response (PR), 60% of stable disease (SD) and a 12 months PFS [56]. Pink et al. reported about 13 patients, only 46% of SD and any objective response. With adriamycine alone the PFS was 3 months. With adriamycine and ifosfamide the PFS improved 8 months [57].

In a pediatric population Casanova et al. described 8 patients who were treated with polychemotherapy based on anthracyclines (2 VACA, 3 VAIA, 2 CEVAIE and 1 CEVAIE followed by high-dose chemotherapy with stem cell rescue). The response to primary chemotherapy was evaluable in 7 patients and was a complete response (CR) in 2 patients, PR for one, so 37% had at least a PR. No response with VACA [58].

About other cytotoxic agents, Frezza et al. described a RR of 23% and a 5 months PFS with gemcitabine-based on 30 patients. Pink et al. reported also the activity of gemcitabine-docetaxel in 13 patients. One CR, 6 PR and 3 SD with a 8 months PFS [57]. About vinorelbine, one case-report described a complete remission of pulmonary metastases [59] and in a retrospective analysis of vinorelbine chemotherapy for

patients with previously treated STS, one of the 2 ES had a PR and received vinorelbine during 27.4 months [60].

2.6.5.2 Other Agents

Pazopanib: a multikinase inhibitor that interferes with the vascular endothelial growth factor and platelet-derived growth factor pathways. In PALETTE study the median PFS favored the pazopanib compared with placebo (4.6 versus 1.6 months), although no statistically significant OS benefit was observed (median OS 12.6 versus 10.7 months) [61]. This results led to approve pazopanib for the non adipocytic soft tissue sarcomas after failure of at least one line of chemotherapy. One case-report described a partial response in a multiple lung metastases of an ES treated for 30 months with pazopanib [62]. But in the largest recent study, the value of this drug seems limited, no objective responses were reported in 20 ES [55].

Paoluzzi et al. described a partial response after 4 cycles of nivolumab and pazopanib in a man with a lung metastasis ES progressing on pazopanib [63].

Trabectedin is approved in the UE for advanced STS previously treated [33].

2.7 Conclusion and Therapeutic Strategy

Due to the rarity of this disease, any suspicion of ES have to be confirmed by a pathological expert validation from a sarcoma reference center. In case of localized resectable disease surgical approach should be the first choice of treatment. Amputation seems to be reserved for tumors not otherwise adequately resectable. ILP can be discussed in locally advanced or multifocal ES.

In the metastatic setting, cytotoxic agents have shown limited activity. EZH2 inhibitors may represent a new therapeutic option. Additional studies are needed to determine their potential in combination with other agents.

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Chapter 3
PEComas: An Uncommon Family of Sarcomas Sensitive to Targeted Therapy

Patrick Soulié and Céline Charon Barra

3.1 Introduction

PEComas are very rare mesenchymal tumors composed of histologically and immunohistochemically distinctive perivascular cells of variable spindle to epithelioid morphology (PECs) [1]. This heterogeneous family of tumors is defined by the WHO classification of tumours of soft tissue and bone (2013) as tumors composed of distinctive perivascular epithelioid cells that show myomelanocytic differentiation in immunohistochemistry. These cells have a unique immunohistochemical profile and typically express both melanocytic markers and smooth muscle markers. However, these lesions are very heterogeneous. Some are not epithelioid, some are not exactly perivascular and some are even HMB45 negative.

PEComas are more common in women than in men (sex ratio 6:1) with a peak in young to middle aged adults [2]. They also have been reported in children, the female predominance becomes apparent only in adolescence, suggesting again hormonal influence in their development [3].

The concept of a family of related tumors (AML, CCST and AML) defined by the presence of distinctive PECs which are reactive with melanocytic markers and contain premelanosomes was first proposed by *Bonetti* in 1992 [4]. In 1996, Zamboni et al. suggested the acronym PEComa for these lesions [5]. It has evolved over the last century, described over the years under a variety of names, reflecting different clinical and pathologic characteristics [2]. Renal angiomyolipoma (AML) was first described

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in 1900 (*Grawitz*) while its association with the tuberous sclerosis complex (TSC) was observed as early as 1911 [6].

The large PEComas family has subsequently included AML of kidney and liver, clear cell "sugar" tumor (CCST) of the lung initially described by Liebow and Castleman in 1963, lymphangioleiomyomatosis (LAM), primary extrapulmonary sugar tumor (PEST), *c*lear cell myomelanocytic tumor affecting lung or lymph nodes of the falciform ligament/ligamentum teres (CCMMT), abdominopelvic sarcoma of perivascular epithelioid cells and a variety of other tumors which share ultrastructural and histologic similarities [7–9]. These lesions show considerable morphologic overlap, suggesting they are variants of a single entity but with significant clinical differences [10]. Finally, PEComas have been described during the last decades in a wide variety of visceral and soft-tissue sites, including the abdomen and pelvis (genitourinary tract, gastrointestinal tract), the retroperitoneum (sclerosing variant) but also in skin and bones [10–12]. They are then termed PEComas NOS (not otherwise specified).

Although there is a strong association between the TSC, AML and LAM, this link is much less clear for the rarer PEComas which usually occur sporadically. More recently, it was described that a subset of PEComas harbors transcription factor E3 (TFE3) gene rearrangements which appear to be mutually exclusive to those associated with TSC. Clinically, most PEComas (other than AML and LAM) follow a benign course and do not recur after complete surgical resection. Surgery remains the key treatment when possible. However, a subset of these tumors will have malignant behavior with either locally invasive relapses or distant metastases, most commonly in the lungs.

3.2 Morphological, Immunohistochemical Features and Differential Diagnosis of PEComas

3.2.1 The Origin of Perivascular Epithelioid Cells (PECs)

PEComas are mesenchymal neoplasms of uncertain histogenesis. Cell of origin remain obscure because no normal counterpart showing the dual phenotype of smooth muscle and melanocytic differentiation has been formally found.

Nevertheless, some explanations were suggested.

The first papers raised the hypothesis that these lesions originated perhaps from the walls of blood vessels, derived from a peculiar and distinctive type of smooth muscle cell able to express myoid and melanoma-associated markers [4].

Indeed, the identification of myofilaments and melanosomes by electron microscopy, correlated with the HMB45 and smooth muscle actin expression raised the hypothesis that the cell at the origin of AMLs could be a cell related to pericytes with melanocytic differentiation [13].

Then, it was said that PEComas could derivate from pluripotent neural crest stem cells, able to differentiate into both myoid and melanocytic cells during embryological development. These origins could also explain that PEComas are described in many sites of the body [14].

These precursors express particularly Neuroglia-2 (NG2) and L1 (a neural cell adhesion molecule), which have both been highlighted in AMLs but not in renal carcinomas by Lim et al. [15].

Telocytes could be another proposition because they are found in many anatomic sites and they have a wide range of functions according to their location. These cells could be at the origin of PEComas like GISTs which share a similar phenotype. They express several markers as CD117, CD34, Smooth Muscle Actin, PS100 and VEGF [16].

The last potential cells could be mesenchymal stem cells (MSCs) because several phenotypic stem cell markers are detected within the PEComas. The immunoexpression is significant for CD29, CD44 and ALDH1. In addition, they are multipotent and widely distributed [17].

3.2.2 A Broad Morphological Spectrum

Grossly, PEComas usually form tan-grey well circumscribed masses, solid and firm. Tumor size ranges widely. They could be altered by hemorrhage, myxoid or cystic changes and focal foci of necrosis.

Cellularity can be variable but the perivascular growth pattern is quite characteristic. Tumor cells seem to replace the muscular wall of the arborizing blood vessels and are thereby closely in relation with the endothelium. They are arranged in nests and short fascicular patterns around many and delicate vessels with reduced stroma. Commonly, cells show epithelioid cytology with clear to eosinophilic granular cytoplasm. They have centrally located round to oval vesicular nuclei with a fine nucleolus. The mitotic activity is usually low (0-1 per 50 HPF high power fields).

But there is a considerable variety of appearances for this single entity.

The spectrum ranges from purely spindled to purely epithelioid forms, and the proportion between both components could be extremely variable. Cells are usually more epithelioid near vessel walls and become more spindled away from vascular channels.

Necrosis, atypia with variable degrees of nuclear pleomorphism, macronucleoli and intranuclear pseudoinclusions may be seen occasionally. Multinucleate giant cells (to attach to degenerative nuclear atypia) and “spider cells” (seen in adult cardiac rhabdomyoma) are possible.

Cells may look like adipocytes or lipoblasts by accumulating amounts of lipids droplets.

Some, in anecdotal cases, also have sex-cord-like features [18, 19].

Sclerosing PEComas, a distinctive pathologic variant, arise most frequently in the pararenal retroperitoneum of middle-aged women [20]. Thick hyalinized bands separate epithelioid tumor cells in a trabecular growth pattern. They have an indolent course.

Melanin pigmented PEComas are described. In a series of 30 hepatic angiomyolipomas, Tsui et al. noted five cases with pigmented foci. Melanin pigment could be highlighted by Masson-Fontana staining in these cells in oncocytic or pleomorphic cells [21].

The TFE3 translocation-associated PEComas form a distinct subgroup. (see below) TFE3 plays a role in the acquisition of specific morphology. These PEComas are composed with large, epithelioid and clear eosinophilic cells, without pleomorphism and mitosis. Cells adopt a nested to alveolar pattern around vessels Spindle shaped cells are absent [22].

Another morphological presentation has recently been reported in the literature. These are fibroma-like PEComas, associated with TSC mutations. They are similar to soft tissue collagenous fibromas with the HMB45 reactivity of PEComas, which is not seen in other fibromas [23, 24].

3.2.3 Immunohistochemical Profile

It is now recognized that PEComas usually co express melanocytic and, in a very particular way, smooth muscle markers but their expression however varies with their morphology. The spindle shaped cells are more positive for muscle markers while epithelioid shaped cells have a strong positivity for HMB45 and less with actin. Moreover, the immunostain is often focal (<50% of cells).

HMB45/gp100 protein (epithelioid human melanoma black 45) is a monoclonal antibody that stains premelanosomes and immature melanosomes. Indeed, HMB45 is considered currently as the most sensitive antibody [25]. However, this antibody is not highly specific and could be detected in a wide variety of lesions such as benign or malignant melanocytic lesions, melanotic schwannoma, clear cell sarcoma of soft tissue, pigmented dermatofibrosarcoma protuberans, some leiomyomas, few rare medullary thyroid carcinomas, occasional non-small cell lung cancer or even some breast carcinomas [26].

Although smooth muscle actin was commonly positive, some PEComas could be negative in few cases [12].

Desmin is less often positive (approximately 25–30% of cases). They same results are observed with S100 protein [22]. Cytokeratins are usually negative as SOX10.

The level of expression of these previously mentioned antibodies were found in the study of Folpe et al. [22]: all their 61 cases are HMB45 positive, 59% are smooth muscle actin positive, 41% are Melan A (melanoma-associated antigen MART-1) positive, 31% express desmin and 11% stain with S100 protein [19]. Comparable results are listed by the team of Acosta [27]. Their 20 aggressive PEComas of the uterine corpus express all HMB45, Melan in 80% of tumors, smooth muscle actin in 84.6% of cases, muscle-specific actin in 66.7% and desmin in 55.6% of these lesions.

MiTF (Microphtalmia-associated Transcription Factor) is a nuclear basic helix–loop–helix leucine zipper protein encoded by the microphthalmia gene (chr 3p), which plays a great role in embryonic development and in postnatal viability of melanocytes. Generally, a diffuse and homogeneous nuclear staining is noticed in a large number of cells. MiTF has a sensitivity and a specificity equivalent to HMB45 and Melan A in the family of PEComas, that's why it could be a new useful marker to add into the classical immunohistochemical panel. but it must be interpreted with caution [28, 29]. We must keep in mind that this antibody reacts with a large range of normal tissues and their derived neoplasms: melanocytes, macrophages, osteo-

clasts, lymphocytes, fibroblasts, schwann cells, smooth muscle cells. Clear cell sarcomas, atypical fibroxanthoma and undifferentiated pleomorphic sarcoma (UPS) were also positive for example [30, 31].

Cathepsin K is a lysosomal papain-like cysteine protease which is a transcriptional target of the MiTF family and involved in bone resorption through osteoclasts. This antibody was recently described as a more sensitive but rather less specific marker for PEComas. A high percentage of cells react with this antibody [29, 32, 33]. Its expression in carcinomas is low except for some Xp11 translocation renal carcinomas (CCR). But, carefully, Cathepsin K is also expressed in various mesenchymal neoplasms: alveolar soft part sarcoma, granular cell tumor, melanoma, histiocytic lesions, GIST, angiosarcoma and Kaposi sarcoma, giant cell tumor of bone or tendon sheath, liposarcomas, in a small proportion of leiomyosarcomas... The context and the morphology are very important and are to be included in the global analysis [34].

CD117 (C KIT) expression is very rare but seen in some lesions [35, 36]. CD117 is a 145-kDA transmembrane tyrosine kinase growth factor receptor protein for stem cell factor. CD117 is present in hematopoietic stem cells, mast cells, germ cells, Cajal cells and melanocytes. Thereby, tumor derived from these cells expressed this marker. This possible cytoplasmic stain, sometimes strong and diffuse, highlights an important differential diagnostic problem between PEComas and GIST. On the other hand, Gastro Intestinal Stromal Tumors (GIST) never express any melanocytic markers and are often CD34 positive. The positivity of the Phospho-p70 S6 Kinase antibody may also be a good indicator of the activation of the mTOR pathway.

A new antibody has recently been described as useful for their diagnosis. It is PNL2 whose target is the somatostatin receptor. PNL2 is sensitive and specific for both melanomas and PEComas. Its cytoplasmic staining is more diffuse than HMB45, therefore very useful on microbiopsy. It is also more intense in sclerosing PEComas of retroperitoneum (100% of cases) or malignant PEComas with epithelioid cytology (83% of tumors) [37].

Immunohistochemistry for the C terminus of *TFE3* protein is a sensitive and specific marker of tumors which have gene fusions involving the TFE3 transcription factor. The positivity in immunohistochemistry is not necessarily correlated with the TFE3 translocation on fluorescent in situ hybridation (FISH). FISH is recommended for confirmation, particularly when the staining on slides is weak. TFE3 is ubiquitously expressed at low levels and moderately increased TFE3 protein expression is not necessary a formal indicator of the molecular change. The risk is detecting native TFE3 protein by IHC in the absence of a true TFE3 gene fusion [38]. For example, Argani P et al. found 13% of TFE3 rearranged PEComas by FISH (4/29 cases) All their cases showed very strong nuclear immunoreactivity [39]. These would be a part of the group of PEComas negative for muscular markers (smooth muscle actin) [40].

3.3 The Spectrum of PEComas Family

PEComas are considered ubiquitous tumors and may arise in almost any location. Some members of the PEComa family (specifically AML and LAM) occur in the context of TSC syndrome.

3.3.1 Angiomyolipoma (AML)

Renal AML is the most frequent member of the "PEComa" family with a female predominance. AML represents less than 1% of renal tumors.

Classic AML is the most common mesenchymal tumor of the kidney.

The great majority of AML show triphasic features (Fig. 3.1). They are classically composed with thick-walled blood vessels, clusters of cells with intra cytoplasmic lipid accumulation and irregular bundles of smooth muscle like spindle cells. But all components may be present in varying proportion and may predominate. These lesions could even be monophasic, leading to diagnostic confusions with lipoma or liposarcoma, leiomyoma or leiomyosarcoma, and even a vascular malformation. This is all the more misleading when we know that some AMLs can express MDM2 (23% to 40% of fat-predominant AMLs) [41, 42]. Leiomyomas do not have prominent vascular or adipose component and are negative for melanocytic markers; leiomyosarcomas are more invasive lesions with severe atypia.

But others morphologic variants of AML have been reported: oncocytic, clear cell or cystic change or prominent sclerosis [43–46]. These cysts are lined by hobnail epithelial cells underlined by compact cambium-like layer of stromal cells.

AML is common in patients with TSC, found in 60–80% of them and are the most frequent cause of death in adults with this disease [47]. They are also seen in 33–50% of patients with sporadic lymphangioleiomyomatosis (LAM) [48]. In patients with TSC, renal AML are found in the third and fourth decades of life, being usually multiple and bilateral, often associated with cysts. However, 80% of patients with AML do not have TSC. Sporadic AML occurs in older patients with a mean age of diagnosis of 45–55 years, being single, unilateral and larger than those related to TSC [49]. Angiomyolipoma form a well demarcated and highly vascularized mass, which grows slowly and is often asymptomatic at first. Pain, hematuria or fever occur later. When this lesion expands, there is an increasing risk of developing aneurysms. Two major complications of AML could then be observed: rupture and retroperitoneal hemorrhage which can be severe and progressive renal dysfunction which can lead to renal failure.

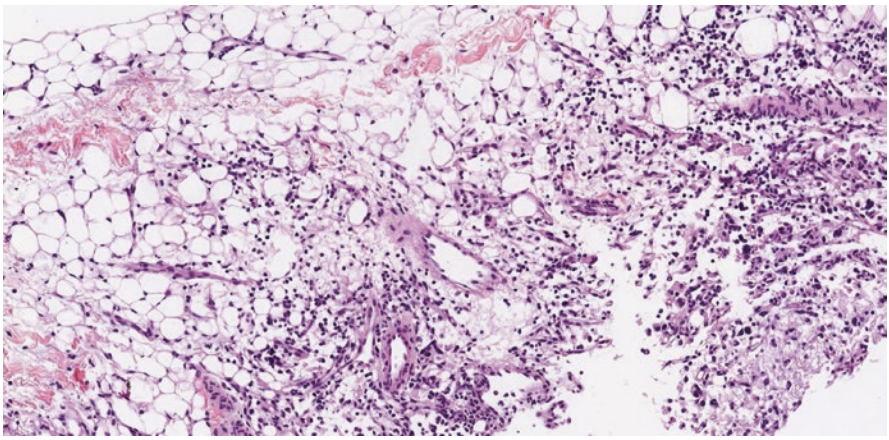

Fig. 3.1 The triphasic features in AMLs (×20)

For a long time, renal AML has been described as a hamartoma, but it is now considered as a clonal mesenchymal lesion representing a neoplastic process [10]. Chromosomal imbalances are common in renal AML. The 5q33-q34 region may contain a tumor suppressor gene, major in the pathogenesis of some lesions [50].

Invasion of regional lymph nodes and extension into retroperitoneum, the renal vein or the vena cava have been noted although the lesion has a benign course. These features indicated multifocality rather than metastasis. However, malignant AML in kidney exists. It is rare but increasingly documented, associated with lung, liver or abdominal metastases [10, 51–54].

Most malignant AMLs have an epithelioid morphology (Fig. 3.2b). They consist of at least 80% of epithelioid cells. They represent about 8% of AMLs [54] and one-third of "atypical" epithelioid AMLs have been reported to show local recurrence and/or distant metastases [55].

In his large series, Brimo observed malignant outcome with local recurrence and distant metastasis in 26% of 34 epithelioid AML with atypical features [51]. Criteria for malignancy in epithelioid AML have been suggested including: (1) ≥70% of atypical epithelioid cells, (2) ≥2 mitotic figures per 10 high-power field, (3) atypical mitotic figures and (4) necrosis; the presence of 3 or all of these features was highly predictive of malignancy.

In another series of pure epithelioid AML, metastasis occurred in 16 of 33 cases (48.5%) [52]. Here, prognostic features were: (1) association with TSC or concurrent AML, (2) tumor size >7 cm, (3) necrosis, (4) extrarenal extension/renal vein invasion and (5) carcinoma-like pattern. Patients with 1 feature had low risk (15%) of progression, those with 2, or 3 had intermediate risk (64%) while the presence of 4 or 5 features was associated with major risk (100%).

The criteria are still a little different in the team of Zhan et al. The coexistence of ≥5 of the 8 following criteria (size ≥ 5cm, metastasis, infiltration, necrosis, ≥50% atypical epithelioid cells, cytologic atypia, atypical mitosis and vessel invasion) can predict their malignancy. Their score was established from 17 cases collected in literature and confirm on their own two cases [56].

Molecular criteria of aggressiveness have also been reported.

p53 gene is recognized as a tumor suppressor gene and his mutation may play an important role in the malignant nature of epithelioid AML. It is reported that atypical epithelioid cells in renal AML overexpressed p53 in immunohistochemistry and

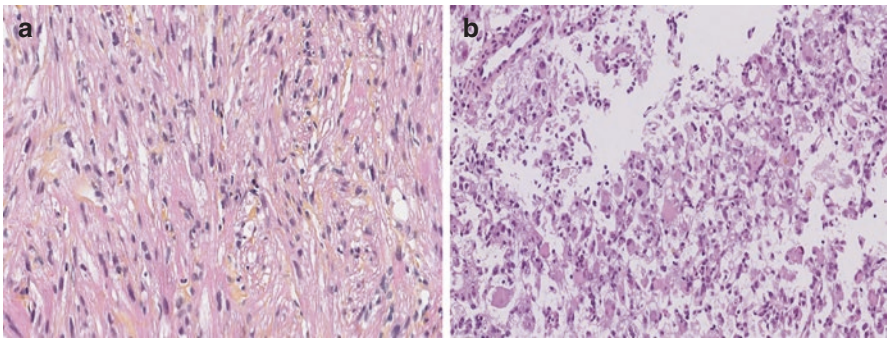

Fig. 3.2 spindle cells AML (**a**, ×20), epithelioid shaped AML (**b**, ×20)

this abnormality is directly correlated with p53 mutation by molecular analysis. These types of mutation, however, are absent in typical AMLs or normal renal tissue used as controls [57, 58]. The same data were found by Li J. and colleagues who identified p53 gene alteration in a primary renal lesion and also in pulmonary metastasis [59]. All these findings are not surprising knowing the major role of p53 in maintaining the integrity of the genome. But mutations alone do not explain p53 nuclear immunoreactivity. Other mechanisms may inactivate p53 which may result in higher protein expression in these tumors [60].

It's also interesting to look at MDM2 (Murine Double Minute 2, an E3 ubuquitin ligase) which induces p53 degradation (negative regulation of TP53 tumor suppressor pathway) and, consequently, cell cycle progression. In an article, by the way, the authors point out that MDM2 is more strongly expressed in metastases than primitive tumors. This expression is correlated at least partially with a proven amplification of the gene. This could potentially promote tumor progression [61].

Malignant PEComas with both sarcoma-like and carcinoma-like morphology have also been reported to arise in preexisting benign AML [62, 63].

Oncocytoma, renal carcinoma, CHC or melanoma must be proposed as differential diagnosis with epithelioid AMLs [64]. AML may even been found simultaneously in association with renal cell carcinoma, especially clear cell carcinoma of the kidney, which brings an additional difficulty in the diagnostic process [65].

Extrarenal sites are also identified. Apart from kidney, liver is the most likely organ involved by AML (8% of all AMLs). Hepatic AMLs were first reported in 1976 by Ishak. Up to 10% are associated with TSC [21, 66]. Most lesions were discovered incidentally. They form an intra parenchymatous or a pedunculated asymptomatic mass. In liver, AMLs are more frequently composed of epithelioid cells variably pleomorphic and are often benign. They often show extramedullary hematopoiesis.

3.3.2 Lymphangioleiomyomatosis (LAM)

LAM is a rare neoplastic multisystem disease. It occurs predominantly in the lungs but extrapulmonary involvement has been reported in lymph nodes and lymphatic ducts (pleura, posterior mediastinum, upper retroperitoneum, mesentery, pelvic cavity) and several other organs (uterus) [67, 68].

LAM shows an extreme sex ratio, affecting almost exclusively women with a mean age at diagnosis of 35 while being extremely rare in prepubertal girls [69, 70]. Few cases were reported in men. It occurs sporadically (s-LAM) or as a part of tuberous sclerosis complex (TSC-LAM). Sporadic LAM is rare and its prevalence varies from 1 to 7.4 per million women [71, 72]. LAM occurs in 30–80% of women with TSC and increases in prevalence with increasing age [73, 74]. LAM is the third cause of death in patients with TSC. Patients with sporadic LAM may have renal AML, axial lymphadenopathy, abdominal lymphangiomyomas but no other features of TSC. TSC-LAM and s-LAM are associated with angiomyolipomas in 93% and 50% of cases, respectively [74].

Proliferation of abnormal bundles of smooth muscle-like PEC, HMB45 positive, around bronchial lymphatics, interlobular septa and pleura is the cause of pulmonary LAMs.

The origin of LAM cells has not been established but it may be the lymphatic system [70, 75]. In women with LAM, identical mutations of TSC2 have been identified in abnormal lung and renal cells, but not in normal cells, suggesting the same origin for LAM and AML. It has been proposed that LAM results from "benign metastasis" of AML cells to the lungs [76].

While LAM was originally considered as a benign disease, more recently it was reclassified as "a low-grade, destructive, metastasizing neoplasm" [77]. Patients with LAM usually develop progressive emphysematous cystic lung destruction with dyspnea, pain and recurrent pneumothorax, chylous collections and occasional hemoptysis. Dilatation of airways is due to the activity of matrix metalloproteinases produced by the cells. Pulmonary failure finally leads to transplantation.

Extrapulmonary LAMs are much larger because these lesions contain multiple cysts filled with chylous fluid. The compression of thin walled lymphatic vessels by cells arranged in fascicles results in obstruction of the flow of lymph or chyle [78].

3.4 Other PEComas (NOS)

3.4.1 Particular Forms

3.4.1.1 Uterine PEComas

One of the most common sites for PEComa-NOS (others than AML, LAM and CCST) is the female genitourinary tract and more specifically the uterus (about 20% of cases). But only less than 150 cases have been reported [22, 29, 79]. PEComas of the gynaecological tract are rare tumors which were first recognised and diagnosed within the last 20 years [80]. These tumors occur most often in middle aged patients (median age 38 years) with a female predominance (sex ratio F/M 7:1). Symptoms are not specific. Tumors are revealed by abnormal vaginal bleeding, abdominal pain or mass. The majority are sporadic uterine tumors. Other sites involved are cervix, vagina, adnexa, broad ligament, vulva and ovary [81]. Some cases of PEComatosis have also been described in the gynaecological tract [82]. Only a small minority (9%) of gynecologic and soft tissue PEComas are TSC-associated [22]. More recently, some cases of TFE3 translocation-associated PEComas have also been reported in ovary, vagina and uterus [38].

The differential diagnosis between uterine PEComas, leiomyomas and leiomyosarcoma variants still remains a challenge for pathologists [79, 80]. PEComas and some epithelioid smooth muscle tumors of the uterus have overlapping morphologic and immunophenotypic features. Smooth muscle cells are generally centered by elongated cigar shaped nuclei and have diffuse cytoplasmic eosinophilia. They make long fascicles arranged in right angles. Thick walled vessels and cleft like spaces are seen within the proliferation. Even if some morphological differences may be observed, the diagnosis is especially difficult because PEComas show a myoid immunophenotype (actin, desmin). In addition, HMB45 could also be detected in leiomyomas, leiomyosarcomas and even in normal uterine muscle cells. HMB45 expression in LMS is present focally in a minor percentage of tumor cells. Should PEComas finally be considered as distinct entities? Are sporadic

uterine PEComas only uterine epithelioid smooth muscle tumor with melanocytic marker immunopositivity? These hypotheses are always discussed and require being careful [83–85].

The distinction between PEComa and some endometrial stromal sarcoma (ESS) could also be difficult, especially in particular presentations. Low grade ESS consists of a proliferation of cells with a phenotype of stromal cells of the proliferative endometrial stroma, arranged around spiral arteriole-like vessels. This lesion adopts a tongue-like growth pattern with vascular permeation. CD10 is not specific for ESS and some cases were described to express HMB45 with variable frequency and intensity. It could be problematic in metastatic sites, leading in a false diagnosis of melanoma or PEComa [86]. The detection of a rearrangement of PHD finger protein (PHF1) gene on chromosome 6 or a translocation (7; 17) (p15; q21) is found in some low-grade ESS (50–65% of all the cases). The translocation involved JAZF1-SUZ12 is identified in 80% of rearranged cases. High grade ESS are usually negative for hormone receptors and diffusely positive for cyclin D1. They often harbor a specific (10; 17) translocation which results in the NUTMN2 fusion product. Other uterine sarcomas with aggressive behavior harbor alterations in the BCOR gene (gene fusion ZC3H7B-BCOR or internal tandem duplications). BCOR immunohistochemistry is then interesting and often positive [87, 88].

Vang et al. come to classify uterine PEComas into two groups. The first group (group A) is morphologically similar to low grade ESS with HMB45 expression and only focal expression of smooth muscle markers. The second group (group B) is morphologically similar to epithelioid smooth muscle lesions with small level of HMB45 positive cells. A continuous histological spectrum with group A PEComas at one end and epithelioid smooth muscle lesions at the other hand has to be considered [89].

From a number of single cases reports and small cases series, it appears that the clinical behavior of these PEComas is varied and ranges from benign to aggressive malignant fashion with distant metastasis [9, 90]. The common metastatic sites of uterine malignant PEComas are, by hematogeneous dissemination, the lungs, liver and bones. Cases with lymph nodes metastases are very few. Uterine rupture leads to the development of multiple pelvic implants called PEComatosis [27].

How to predict for pathologists the biological behavior of PEComas? Firm criteria for malignancy remain uncertain. In an effort to better predict clinical outcome, risk stratification criteria based on pathologic features have been proposed for this subset of rare non-AML/non-LAM PEComas. These classifications are numerous but must be validated on larger series. Folpe et al. evaluated 26 cases of PEComas from soft tissue and gynecologic tract from their archives and in combination with a review of literature suggested in 2005 criteria for malignancy, including size >5 cm, mitotic count ≥1/50 high power fields (HPFs), necrosis, infiltrative margins, vascular invasion, high grade nuclear atypia or high cellularity. Based on these criteria, the current prognostic classification system was proposed to delineate three risk categories (from benign to malignant potential). The presence of 2 or more of these criteria indicates a high risk of clinical evolution. These criteria must be applied only to PEComas other than classical AMLs which could have large size, necrosis, atypia and still remain benign. The presence of giant multinucleated cells has no pejorative meaning, but it is more prudent to classify them as having “uncertain malignant potential” [22].

When applying to a larger group (93 cases selected / 234 cases extracted from the English literature), 94% are classified as malignant according to Folpe's risk stratification. These criteria have therefore been widely adopted. Since, this classification system was also assessed in other series of PEComas of gynecologic tract and appears to be validated.

No recurrence is noted by Bleeker et al. if the tumor size is less than 5 cm without any other risk factor. For them, the two main factors (size ≥ 5cm and high mitotic count) seem to predict a higher risk of recurrence after surgery, as shown in the Table 3.1 [90].

Fadare has also reviewed 41 reported cases of uterine PEComas and concluded, on the other hand, that a high mitotic rate (>1/10 HPFs) and necrosis were major predictors of malignancy in this group [91]. Eight (20%) patients had disease recurrence to one to three sites including the lungs, pelvis, lymph nodes, liver or bones.

More recently, as previously noted, Schoolmeester applied the Folpe criteria to 16 gynecologic cases (13 were from uterine origin) and proposed a modified system in which only the statistically significant histologic features associated with adverse outcome were used (gross size ≥5 cm, high grade nuclear atypia, necrosis, lymphovascular invasion, mitotic index ≥1/50HPFs). Benign and uncertain malignant potential categories are melted together. Malignant cases must have four or more worrisome features [29]. They reach a sensibility and specificity of 100%, classifying all tumors with malignant outcome as malignant. In this series with a mean follow of 26 months (1–156), time to recurrence varied from 1 month to 6 years. It has already been reported that PEComas may present recurrence with distant metastasis many years after their initial diagnosis [92]. The use of careful long term follow up is warranted, especially for tumors with aggressive, high risk criteria.

Then, Conlon et al., in 2015, based on their 78 cases of uterine PEComas, proposed a modified Folpe grading [80]. Necrosis is sufficient enough to consider malignancy as shown in Table 3.2.

Finally, Bennett et al. validate the Schoolmeester's score on 32 PEComas. Three of the 5 features are enough to classify a PEComa as malignant [93].

Table 3.1 Prognostic classification (adapted from Folpe et al., Bleeker et al. [90])

High risk morphological features	
(a) Size > 5 cm	
(b) Infiltrative growth pattern	
(c) High nuclear grade and cellularity	
(d) Mitotic rate > 1/50 HPFs	
(e) Necrosis	
(f) Vascular invasion	
Risk category	
1. Benign	<2 high risk features and size <5 cm
2. Uncertain malignant potential	Size ≥5 cm with no other high risk features OR nuclear pleomorphism/multinucleated giant cells only
3. Malignant	2 or more high risk features

Table 3.2 Prognostic classification (adapted from Folpe criteria, Conlon et al. [80])

Benign	No or a single worrisome feature (invasive edge, size ≥ 5cm, mitotic count > 1/10HPF)
Uncertain malignant potential	One worrisome feature that includes isolated marked atypia, size > 10cm or mitotic count > 3/10HPF
Malignant	Any necrosis or two worrisome features

Despite all this, surgery remains the mainstay of therapy for localized tumors but surgical resection of oligometastatic disease has also been of benefit in recurrent disease [94].

3.4.1.2 PEComas of the Gastrointestinal (GI) Tract

20–25% of all PEComas arise in the GI tract which is the second site behind gynecological tract.

Clinical manifestations are not specific. PEComas are detected by pain (35%), melaena, rectal bleeding, obstruction, weight loss and anemia. 70% of cases show a pure epithelioid cytology. The association Melan A with smooth muscle actin (SMA) expression was the dominant pattern (60%) followed by the couple HMB45 / SMA (59.3%) [95].

Doyle et al. reported the largest series of GI PEComas, which included 35 cases identified over a 26-year period. In contrast to PEComas occurring at other sites, GI PEComas do not exhibit gender predilection [96]. The most common site of involvement was the colon followed by the small intestine. 83% and 89% respectively express at least one muscle marker and one melanocytic marker. 27 of 35 cases coexpressed at least one muscle marker and one melanocytic marker. A single case is associated with TSC. PEComas of the GI tract appear to show variable biological behavior, ranging from benign tumors to aggressive sarcomas, and more than 1/3 of patients in this series were known to develop metastases. The presence of marked nuclear atypia, diffuse pleomorphism and mitotic activity (≥2 mitoses per 10 HPF) were significantly associated with metastatic risk.

The differential possible diagnoses are multiple. *Abdominal GISTs* are very frequent and must be absolutely taken into account. GISTs lack the perivascular concentric network and vessels are less numerous. Epithelioid and spindled cells have more eosinophilic cytoplasm. Melanocytic markers are negative and CD34 stain is often present in GISTs. The difficulty is that C KIT could be positive in PEComas and GIST could express Actin and Desmin [97–99].

In order of frequency, we also have to make the distinction between *carcinomas* and PEComas which can mime renal clear cell carcinomas or hepatocellular carcinomas. The diffuse cytokeratin expression and the negativity for melanocytic markers in carcinomas are helping in the differential diagnosis. In metastatic clear cell renal carcinoma, diffuse expression of EMA and PAX8 is useful. Epithelioid PEComas may be confused with *adrenal cortical neoplasms or paraganglioma*. Melan A is present in ~90% of adrenal cortical neoplasms but Desmin and HMB45 are absent. The positivity of Synaptophysin, Calretinin and Inhibin antibodies are detected in this entity. Paragangliomas have PS100

reactive sus tentacular cells which surround nests of positive cells for chromogranin and synaptophysin.

Malignant melanoma must not be especially forgotten. S100 protein, SOX10 and C KIT frequently show strong positivity; smooth muscle actin and desmin are negative. A high mitotic rate, marked atypia, possible necrosis, angiolymphatic invasion and other synchronous lesions are associated.

Alveolar soft part sarcoma (ASPS) is rare in gastro intestinal tract. Their solid form could lead to an erroneous diagnosis. Their eosinophilic polygonal cells have distinct cell borders, higher nuclear grade, large prominent nucleoli and sometimes intracytoplasmic granules or rhomboid crystals. Lymphovascular invasion are frequently seen. TFE3 nuclear expression reflect an unbalanced translocation der (17) t (X; 17) (p11; q25) involving ASPSCR1 and TFE3. Actin, Melan A and HMB45 are almost negative. Desmin and PS100 can be focally expressed. For note, they share this ASPL-TFE3 fusion with the Xp11 translocation RCC. The rare *clear cell sarcoma-like tumor of the GI tract contains in* 50% of cases osteoclast-like giant cells. PS100 reactivity is strong but HMB45 expression less consistent. This entity has preferentially a variant fusion gene EWSR1-CREB1 t (2; 22) (q32.3; q12).

Schwannoma and smooth muscle tumors have to enter the discussion, as described before.

To finish, making any distinction with a *clear cell sarcoma* could be difficult. In clear cell sarcoma, the tumor nests are separated by a collagenous stroma and prominent nucleoli are seen. They have a melanocytic phenotype: HMB45, MiTF and PS100 are positive but actin and desmin are consistently negative. Identification of the specific t (12; 22) (q13; q12) resulting in the EWSR1/ATF1 gene fusion can be useful to confirm the diagnosis in more than 90% of the cases. These occur mostly in deep soft tissues of the extremities of young adults.

3.4.1.3 Bladder PEComas

A small number of PEComas have been reported to arise firstly within the urinary bladder and their behavior is not well known. Urinary bladder PEComas occur in middle-aged adults, with a male predominance, suffering from haematuria or pelvic mass [100]. No association with TSC is described while few TFE3 rearranged PEComas were reported. They are quite similar to urothelial carcinoma. The intensity of nuclear TFE3 reactivity is moderated or strong [101].

Major differential diagnoses of these tumors must include carcinoma, melanoma and smooth muscle tumor. Leiomyoma and leiomyosarcoma are the most mesenchymal tumors of urinary bladder in adults, whereas primary melanoma is rare in this anatomical site [102, 103]. A component in situ often persists in the cases of melanomas and sarcomatoid carcinomas. Spindle or epithelioid malignant melanoma express S100 protein. Urothelial carcinoma, metastatic renal cell carcinoma or invasive prostatic adenocarcinoma are reactive with cytokeratins. PEComas can be also mistaken with paraganglioma, GIST, inflammatory myofibroblastic tumor (IMT) or postoperative spindle cell nodule. IMT have chronic inflammation, myxoid stroma and ALK1 expression in many cases revealing a rearrangement of ALK. Finally, a large and appropriate immunohistochemical panel is helpful.

3.4.1.4 Cutaneous PEComas

The first case described in the litterature dates from 2003 [104].

Then, Menzel et al. reported the first series of seven cutaneous PEComas as clear cell myomelanocytic tumor (CCMMT) occuring in extremities of adult females [105]. They have always an epithelioid clear cell morphology are highly vascularized and express HMB45. They react less consistently with myogenic markers and desmin is most commonly expressed in this variant [106]. These dermal PEComas follow a benign course, however, a malignant case has been reported by Walsh and Sangüeza [107].

The main differential diagnoses are rare clear cell histiocytofibroma, benign and malignant melanocytic neoplasms such as balloon cell melanoma (an intra epithelial component is often detected), atypical fibroxanthoma in sun damaged skin in elderly people, metastases of clear cell renal carcinoma and sebaceous carcinoma which are cytokeratin immunoreactivity, clear cell sarcoma of tendons and aponeuroses.

3.4.1.5 Malignant PEComa

As previously detailed, PEComas have a heterogeneous biologic behavior with a majority of tumors pursuing a benign clinical course after their surgical ablation while others are metastatic at the time of diagnosis or will experience relapses after curative surgery (Fig. 3.3). PEC tumors can involve multiple organs that's why distinction between metastatic spread and multifocality can be difficult. Approximatively one-third of the PEComas other than AML and LAM have

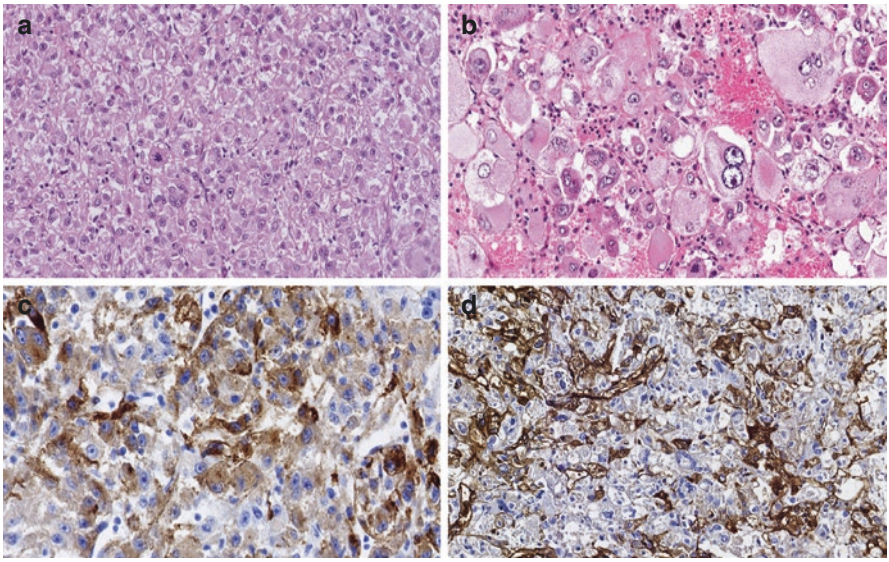

Fig. 3.3 Malignant PEComa (**a** and **b**), HMB45 (**c**) and actin smooth muscle (**d**) positive (×20)

malignant behavior. Malignant PEComas have been observed at various sites including uterus, gastrointestinal tract and retroperitoneum. Folpe and others have identified histological criteria for malignancy (see above). The 18F- FDG PET/CT has shown the potential role in differentiating benign and PEComas [108, 109]. Such imaging could be helpful in staging/restaging for malignant PEComas and guiding treatment with mTOR inhibitors [110].

3.4.1.6 Genetics and Pathogenicity

TSC, a Genetic Disease Associated with AML, LAM and Other PEComa Related with TSC

TSC is an autosomal dominant multiorgan system disorder affecting ~1.5 million people worldwide caused by mutations in either TSC1 (27%) or TSC2 (73%) genes. Purely heterozygous germline mutations as well as mosaic mutations have been identified in TSC patients. Diagnosed from birth through adulthood, this syndrome is characterized by the development of several "benign" tumors called hamartomas in multiple organs including intracranial tumors (cortical tubers, subependymal giant cell astrocytomas[SEGAs]) and extracranial tumors such as cardiac rhabdomyoma, renal AML and pulmonary LAM. While AML and LAM represent a subset of PEComas strongly associated with TSC, most PEComas other than AML and LAM are sporadic and less frequently associated with the TSC [10].

Biallelic inactivation of TSC2 or TSC1 including point mutations, small indels, large genomic deletions and copy neutral LOH (loss of heterozygosity) has been demonstrated in AML and LAM tumors of patients with or without TSC [111].

TSC1 gene on 9q34 and TSC2 gene on 16p13.3 encode respectively for hamartin (140KDa) and tuberin (200KDa) proteins. TSC1 and TSC2 are tumor suppressor genes. TSC1 protein product stabilizes the other TSC2 gene product. It prevents its ubiquitin-mediated degradation by forming a complex. The formation of this hamartin/tuberin heterodimer negatively regulates the mammalian target of rapamycin (mTOR) pathway by inhibiting the activation of S6K.

mTOR plays normally a role in the control of cell proliferation and cellular metabolism. Two multiprotein complexes exist: mTOR complex 1 (mTORC1) which contains Raptor protein (regulatory associated protein of mTOR) and LST8 (lethal with SEC 13 protein 8) and the mTOR complex 2 (mTORC2) which comprises Rictor protein (rapamycin_insensitive companion of mTOR), SIN1 (stress-activated-protein-kinase_interacting protein1) and LST8 [112].

They have also different bioenergetic pathways. mTORC1 promotes glutamine metabolism and mTORC2 correlated with acetate utilization in LAM cells metabolism. mTORC2 acts more on the modeling of the actin cytoskeleton though AKT phosphorylation [113]. Rheb (Ras homolog enriched in brain protein) is a 21-kd member of the RAS family of GTPases. Its active form (Rheb-GTP) interacts with mTOR to form an active complex: mTORC1. This multiprotein complex phosphorylates ribosomal protein S6 Kinase (S6K) and 4E-BP (eukaryotic translation initiation factor 4E-binding

protein) with significant increase of proliferation. In particular, the GAP domain of TSC2 converts Rheb-GTP into Rheb-GDP which inactivates the mTORC1 kinase leading to decreased cell growth. So, TSC1-TSC2 complex is a major negative regulator of mTORC1 activation. An inactivating mutation in either gene leads to a loss of a functional hamartin-tuberin protein heterodimer and to secondary constitutive mTORC1 activation hyperactivation responsible for tumor progression [2, 114, 115].

TSC1 or 2 Gene Alterations in Sporadic PEComas

TSC1 and TSC2 genes also play a great role in the pathogenesis of many PEComas. A significant number of sporadic PEComas show inactivation or loss of TSC2 which leads to activation of the mTOR pathway. Loss of heterozygosity at the TSC2 gene locus has been described in both sporadic and tuberous sclerosis-associated PEComas [111, 116].

Increased levels of phospho-p70S6K -a marker of mTOR activity- and reduced phospho-AKT expression which suggests a disruption of TSC1/2 function has been documented in non TSC-AML but also in extrarenal PEComas [117]. These results suggest that mTOR hyperactivity may contribute to tumor progression. Allelic loss of the TSC2 locus on 16p13 has been reported in sporadic AMLs and PEComas suggesting a potential causal link [118]. A CGH array analysis performed on nine cases of PEComas showed multiple chromosomal imbalances. The frequent deletion of 16p in which the TSC2 gene is located serves to highlight the genetic relation between angiomyolipomas and PEComas as TSC2-linked neoplasms [119].

TSC2 inactivation and TFE3 rearrangement seem to be mutually exclusive with significant therapeutic implication

TFE3-gene fusion was initially reported by Tanaka et al. in a gastrointestinal PEComa.

A subset of PEComas harboring TFE3 gene fusions has been identified [38, 39, 80, 120–122]. TFE3 is a member of the MiT family of transcription factor, located in the short arm of chromosome X (Xp11.2 region). MiTF gene family members induce melanocyte differentiation.

TFE3 gene fusions are known in several types of cancers including alveolar soft part of sarcoma and a subset of renal cell carcinoma (Xp11 translocation-associated renal cell carcinoma). All these neoplasms share similar morphological features.

Three hypotheses have been advanced to explain the role in tumorigenesis by TFE3 translocation: a disruption of the tumor-suppressor activity of TFE3, a novel conformation leading to a novel activity or an upregulated transcriptional activity by the fusion protein [123].

In one study of 38 cases, TFE3 translocations were found in 23% of PEComas analyzed. SFPQ/PSF-TFE3 translocation (t(X; 1) (p11.2; p34)) is the most prevalent gene fusion. A novel DVL2-TFE3 gene fusion was also identified in one case by RNA sequencing (t(X; 17) (p11.2; p13.1)) resulting in TFE3 oncogenic activation. All these PEComas are located in soft tissues. DVL2 encodes a member of the dishevelled (dsh) protein family [124]. PEComas harboring TFE3 gene rearrangements lack the TSC2 alterations and are biologically distinctive [125]. None of the TFE3 rearranged PEComas were TP53 rearranged whereas TP53

mutation is seen in 63% of cases with TSC2 mutation associated [126]. This finding suggests an alternative pathway of tumorigenesis with therapeutic consequences. The use of mTOR inhibitors may be inappropriate in this subgroup.

Rare cases showing amplification of TFE3 have been described [39].

Other Molecular Rearrangements

Other gene rearrangements have been described including RAD51B (DNA repair protein RAD51 homolog 2) in some cases [124]. This novel recurrent RAD51B (14q23-24.2) gene-associated fusion is identified in uterine PEComas exclusively. RAD51 belongs to the family of protein implicated in DNA repair by homologous recombination. RAD51B can be combined to RRAGB (Xp11.21) or OPHN1 (Xq12). Interestingly, RAD51B gene abnormalities are also described in uterine leiomyomasnot. Two other different gene fusions are described: HTR4-ST3GAL1 gene fusion was detected in a single case and RASSF1-PDZRN3 gene fusion was highlighted in another case.

As already said, TP53 mutation is also reported in some cases of pure epithelioid angiomyolipomas and not in classical angiomyolipomas. This alteration in the TP53 pathway could explain their more aggressive behavior [126].

3.5 Management

3.5.1 Surgery

Historically, surgery was the only treatment modality for large and fast growing *renal AML*. Prophylactic subselective embolization has been the other option available. However, any surgery or embolization leads to loss of healthy nephrons. New international guidelines considered embolization should be reserved for AML that are acutely bleeding [127].

For patients with *PEComas other than renal AML or LAM*, standard treatment is wide surgery when disease is localized. However, about one third of patients had advanced, unresectable disease or will develop metastases later. Surgical resection of isolated metastatic lesions has been an effective approach in some cases when patients were rendered disease free.

3.5.2 Chemotherapy

Conventional chemotherapy strategies have not been successful in advanced malignant PEComa with very few confirmed responses [128–131]. Different agents or combinations were tested including those active in soft tissue sarcomas. There are obvious difficulties to perform a therapeutic trial due to the rarity of the disease. Recently, preliminary results of a retrospective multicenter cases series from four

Italian institutes were reported [132]. Data were collected for patients with advanced or metastatic treated with either anthracycline—or gemcitabine-based regimens between 2000 and 2017. Activity was minimal with these cytotoxic agents with a response rate (RR) of 10 and 21% and a median progression free survival (PFS) of 2.8 and 3.4 months respectively in each cohort.

3.5.3 Targeted Therapies

3.5.3.1 Hormonal Therapy

As LAM is a disease of female predominance which occurs in reproductive-age women and may worsen during pregnancy or with exogenous estrogen exposure, it was suggested that hormones such as estrogens and progesterone may contribute to disease pathogenesis [133, 134]. LAM cells also express the estrogen and progesterone receptors. Various hormonal manipulations have been used including oophorectomy, GnRH analogs, tamoxifen or progesterone without clear evidence of efficacy. Despite a number of cases reports, no confident data exist on the efficacy of any antiestrogen strategy for LAM and there has been a lack of controlled trials. Evidence-based recommendations suggest not using hormonal therapy [135, 136]. In breast cancer, preclinical evidence has implicated PI3K/AKT/mTOR pathway deregulation in acquired resistance to endocrine therapy and led to the evaluation of mTOR inhibitors combined with aromatase inhibitors or tamoxifen. In two randomized trials, clinical benefit was demonstrated in patients who received the combination when compared to endocrinal therapy alone [137, 138]. Randomized trial with hormonal therapy alone or with mTOR inhibitors should be considered to better assess the impact of hormonal manipulation in LAM patients [136].

3.5.3.2 mTOR Inhibitors (mTORi)

Multiple inhibitors have been developed for clinical use, either to treat fungal infections, to prevent post-transplant rejection or as antitumoral agents. The efficacy of mTORi has also been explored in patients with a heterogeneous mix of metastatic sarcomas, with only a modest response rate [139]. In patients with metastatic soft-tissue or bone sarcomas and a non-progressive disease on first line chemotherapy, maintenance therapy using an oral formulation of ridaforolimus was also tested in one large, double blind placebo-controlled study; this phase 3 (SUCCEED) demonstrated a statistically significant but clinically small benefit [140]. Finally, it appears that selection of patients according to specific mutations in the PI3K-AKT pathway should be considered to improve the efficacy of mTORi. Activation of mTORC1 through loss of the TSC1/TSC2 repressor complex is a common and critically pathogenic event in the majority of PEComas. Targeting mTOR with specific inhibitors is a rational approach to treating patients with TSC and progressive AML, LAM or SEGA but also those with sporadic PEComas. Encouraging results observed in TSC-deficient mouse

models have prompted clinical studies with rapalogs. The activity of the mTORi sirolimus has first been reported specifically in AML and LAM [141, 142]. Robust knowledge around treatment side effects and dosing existed before they were first given to TSC patients. Sirolimus and everolimus selectively inhibit mTOR signaling with similar molecular mechanisms but with distinct clinical profiles [143]. Prolonged treatment appears to be associated with improved tolerability [144].

mTORi for Renal AML

Four trials using sirolimus have confirmed the efficacy of mTOR targeting with impressive results [145–148]. In these studies, patients received sirolimus at an initial dose adjusted on blood level (3–10 ng/ml) with further increase to a (maximum) target level between (6–15 ng/ml) if the total AMLs volume or the longest diameter of target lesions was not reduced by 10% of the baseline value at 2 months.

After these encouraging initial results, everolimus, an oral inhibitor was investigated in EXIST-2, a multicenter, randomized, double-blind, placebo-controlled phase 3 trial. Preliminary report demonstrated a clear advantage for everolimus over placebo in reducing AML tumor volume (response rate 42% versus 0%) with an acceptable toxicity profile [149]. Long term use of everolimus has been reported and this analysis confirmed the treatment was effective and safe over approximatively 4 years [150, 151]. Renal AML response has improved over time from 42% in the core phase to 58% in the extension phase, while the median period of everolimus exposure has also increased from 8.8 to 46.9 months. Clinically relevant renal AML reductions persisted over time and overall, renal progression was observed in only 14% of patients. AML related complications were uncommon and none of the treated patients experienced bleeding during the study. Median GFR and serum creatinine values remained stable in most patients. Stomatitis, a known event associated with everolimus was the most frequent side effect.

The TSC consensus guidelines recommend mTOR inhibitors as first line therapy for asymptomatic growing angiomyolipomas measuring >3 cm in diameter, whereas selective embolization and kidney-sparing resection are acceptable second line therapies [152].

LAM

Several clinical studies have also demonstrated the efficacy of mTORi in the treatment of LAM [153, 154]. The *MILES* trial was a landmark study for pulmonary LAM involving patients with moderate lung function impairement (defined as FEV1 <70% predicted) [154]. This two-stage, randomized, double-blind trial compared 12 months of sirolimus versus placebo, followed by a 12 months observation period where no treatment was given. Following the first stage, 46% of patients on sirolimus had FEV1 values at or above baseline compared 12% in the placebo group. However, a decline in pulmonary function was observed in both groups during the observation period, suggesting that continuous therapy is required. In the

EXIST -2 study, 29 patients with TSC-related or sporadic LAM received everolimus for a longer period of time (median exposure, 46.9 months); in this subset of patients, a lower than expected rate of decline in lung function was reported [151].

Both sirolimus and everolimus have also been reported to treat successfully extrapulmonary, abdominal or pelvic LAM with several prolonged partial or complete tumor regression [155–157].

The ATS/JRS guidelines for LAM have recently been published and recommend for patients with LAM with abnormal/declining lung function treatment with sirolimus rather than observation and for those with problematic chylous effusions also sirolimus before invasive management [136].

3.5.4 Malignant PEComas

After encouraging activity with sirolimus was observed in patients with AML associated with TSC or sporadic LAM, case reports were published for patients with advanced malignant PEComa treated with either sirolimus or temsirolimus [158, 159]. Several patients have experienced complete responses to rapalogs lasting over a year. Other single or case series were reported some years later which demonstrated major clinical benefit, including sustained complete responses [160–164]. Neoadjuvant treatment with sirolimus has also been reported in one patient with large epithelioid hepatic PEComa with malignant potential with a favorable tumor shrinkage [165]. However, cases of primary resistance were also published [166, 167]. On note, one patient with disease progression with one mTORi was successfully rescued with another [164]. Some authors have explored the correlation between radiological response and molecular profiling. Evidence of mTORC1 activation or genetic alterations in TSC1 or TSC2 were screened either by immunohistochemistry or aCGH. It seems that the combination of genetic alterations in TSC1/2 and staining for pS6-S235-236 may predict response to mTOR inhibitors [161, 163]. More recently, Sanfilippo has reported a larger case series of 39 patients with advanced or metastatic PEComa treated with one mTOR inhibitor (sirolimus, everolimus or temsirolimus) [132]. Again, very encouraging results were produced with a 41% RR and median PFS of 10 months which compared favorably with those obtained with standard chemotherapy previously detailed. The AMPECT trial was the first prospective study ever performed in malignant PEComa. In this study, 34 patients were treated with ABI-009 is an albumin-bound mTOR inhibitor with increased tumor uptake. Among the 31 patients evaluable for efficacy, 42% (13/31) patients had objective response. Median PFS was 8.9 mo (95% CI: 5.5, -). The most common (>30%) nonhematologic treatment-related adverse events (TRAE) of any grade were mucositis (65%), fatigue (53%), nausea/weight loss (35% each), diarrhea (32%); the most common (>15%) hematologic TRAEs: anemia (44%) and thrombocytopenia (18%). Altogether, these results suggested that ABI-009 may represent a promising therapeutic strategy [168].

3.6 Conclusion

PEComas are a very rare subset of sarcomas mostly associated with TSC gene alterations which led to subsequent over-activation of the mTOR signaling pathway. The discovery of such connection has suggested the evaluation of mTORC1-targeted therapy which is now largely used against these tumors. Clinical benefit has been documented in AML patients and encouraging results have been provided for patients with more aggressive malignant PEComa. Correct diagnosis of these tumors is important as genetic counseling and surveillance for diseases associated with TSC should be considered. Targeted therapy with mTOR inhibitors could be proposed in progressive, aggressive tumors but prospective studies are still necessary to expand our understanding of molecular alterations and mechanisms of treatment resistance.

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Chapter 4
Desmoplastic Small Round Cell Tumors

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4.1 Epidemiology and Risk Factors

Desmoplastic Small Round Cell Tumor (DSRCT) is a rare abdominal disease of unknown origin affecting predominantly Caucasian children and young adult males (median age in series between 19 and 27 with extreme reported from 0.5 to 56, Male:female ratio 3.5:1–10:1) characterized by a specific translocation t(11:22)(p13;q12), which fuses the ESWR1 gene to the WT1 gene. The name DSRCT derives from its characteristic histologic findings of clusters of small round tumor cells surrounded by abundant fibrous desmoplastic stroma. The estimated incidence ranges between 0.2 and 0.7 cases per million per year. Fewer than 900 cases have been reported in the literature since its first description in 1989. DSRCT has an extremely aggressive clinical course, most patients having distant metastases at diagnosis, either peritoneal or extra-peritoneal. Despite a multimodal complex treatment, recurrence or progression is common and overall survival is poor.

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4.2 Diagnosis

4.2.1 Clinical Features

DSRCT must be suspected in case of a young adult male presenting with signs and symptoms of peritoneal carcinomatosis with bulky masses. Most patients with DSRCT present with symptoms of abdominal pain or discomfort, bloating, loss of appetite, nausea, constipation, jaundice, and/or weight loss. DSRCT has an extremely aggressive clinical course, with more than 90% of patients having synchronous peritoneal metastases at diagnosis, and 47–53% having synchronous extra-peritoneal metastases (EPM) mostly in located in the lymph nodes, liver and lung. No predisposing factors have been identified yet.

4.2.2 Imaging and Survey

No standard survey is recommended specifically for DSRCT and the diagnostic workup must be made as for any other patient with bulky peritoneal tumor of unknown origin. Although no tumor marker is specific for DSRCT, a complete blood test including liver and kidney function evaluation (to detect either a biliary and/or a urinary obstruction) is mandatory. A complete assessment of nutritional status is also required. Contrast-enhanced CT-scanner is the initial imaging study of choice, revealing multiple disseminated masses throughout the abdomen and pelvis. Magnetic resonance imaging (MRI) can be considered in complement for detailed delineation of pelvic and liver lesions. Positron emission tomography scanner is used to detect distant extraperitoneal lesions, either lymphatic or hematogenous. The diagnosis of DSRCT can only be made on the pathologic examination and sample must be retrieved either by a staging laparoscopy or percutaneous biopsy under imaging. The quality of the sample is critical and enough material should be available for molecular analysis.

4.2.3 Pathology

DSRCT is a rare type of sarcoma belonging to the group of malignant small round cell tumors.

4.2.3.1 Macroscopy

The typical appearance of DSRCT consists of multiple tumor nodules of variable sizeat the peritoneal surface. On cut surface, the tumor is firm grey-white, well delineated or with infiltrative margins.Hemorrhage and necrosis may be observed.

4.2.3.2 Light Microscopy

DSRCT is characterized by nests and sheets of uniform small round tumor cells with round hyperchromatic nuclei, minimal cytoplasm, indistinct cytoplasmic borders surrounded by a prominent desmoplastic stroma composed of fibroblastic cell-sembedded in a loose extracellular material or collagen. Mitotic index is high. Central necrosis is common in large lesions and cystic degeneration can be seen. Some tumors may have neural or epithelial differentiation with rosettes or glandular pattern. Intracyptoplasmic eosinophilic rhabdoid inclusions may be also observed in a subset of cases.

4.2.3.3 Immunohistochemistry

Most DSRCT have a polyphenotypic differentiation by immunohistochemistry, the tumor cells expressing simultaneously epithelial (keratins, EMA), musclar (desmin) and neural (NSE) markersNuclear expression of WT1, derived from the EWSR1-WT1 fusion protein, is observed with antibody detecting the C-terminal portion of the protein, but not the N-terminal portion which is not conserved in the fusion protein. CD99 membranous expression may be observed. Useful negative markers for differential diagnosis include S100, Myogenin and MyoD1.

4.2.3.4 Molecular Biology

DSRCT is characterized by a *EWSR1-WT1* fusion transcript derived from a t(11;22)(p13;q12) translocation, resulting in the fusion of Ewing Sarcoma RNA binding protein 1 (*EWSR1*) gene in 22q12 (a potent transcription factor) and Wilms tumor 1 (*WT1*) gene in 11p13 (a Zinc finger DNA binding domains). The most common chimeric transcript comprises an in-frame fusion of the first 7 exons of EWSR 1 and exons 8–10 of WT1, although other rare variants have been described. Molecular confirmation of the diagnosis is usually performed either by the identification of an *EWSR1* gene rearrangement by Fluorescent In Situ Hybridization (FISH), in association with the clinical and histopathological data, or by the detection of a specific *EWSR1-WT1* fusion transcript by RNA sequencing.

4.2.3.5 Differential Diagnoses

Until the recognized a pathognomonic *EWSR1-WT1* t(11;22)(p13:q12) chromosomal translocation recognizing the disease as a distinct clinical entity, DSRCT may have been misclassified as an undifferentiated malignant tumor of the testes, ovary, mesentery, or gastrointestinal tract, or other small round “blue cell” sarcomas subtypes (Ewing sarcoma, rhabdomyosarcoma, synovial sarcoma). Currently, clinical

and histopathological presentation are in most cases evocative of the diagnosis, which is subsequently confirmed by molecular analysis.

4.2.4 Staging

There is no prospectively validated staging system for DSRCT. The most commonly used staging system in is the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (IUCC) for soft tissue sarcomas with the unintended effect of identifying most DSRCT as stage 4 disease. Most patients having peritoneal metastases at diagnosis, the peritoneal cancer index is used to assess the extent of the disease throughout the peritoneal cavity. For this purpose, the peritoneal cavity is divided in 13 regions (9 for the abdomen/pelvis and 4 for the small bowel) in each of which the size of the largest tumor nodule is measured to define a score (0 if no tumor is seen, 1 if the largest tumor nodule is below than 0.5 cm, 2 if the largest tumor nodule is below than 5 cm and 3 if the largest tumor nodule is above 5 cm). The extent of the disease is calculated by adding the scores of all 13 regions together (ranging from 0 to 39). To integrate the prognostic impact of extra-peritoneal disease, the MD Anderson proposed a composite score based on PCI, regional spread (intra-abdominal), and distant (extra-abdominal) metastases. The proposed a staging was stage 1: PCI below 12, no liver metastasis and no extra-abdominal metastasis, stage 2: PCI above or equal to 12, no liver metastasis and no extra-abdominal metastasis, stage 3: any PCI, liver metastasis and no extra-abdominal metastasis, stage 4: any PCI, extra-abdominal metastasis with or without liver metastasis.

4.3 Treatments

4.3.1 Locoregional Treatment

4.3.1.1 Surgery

Without any randomized studies and very few prospective databases, the level of evidence remains poor. Surgery is the cornerstone of curative intent treatment in DSRCT. Completeness of cytoreductive surgery (CRS), i.e. removing all macroscopic (visible) peritoneal tumor implants through a series of visceral resections, is the greatest prognostic factor. In every reported series, a major difference is seen between overall survivals (OS) of patients after macroscopically complete CRS (3-year OS of 58–71%, median OS of 31–36 months) and after incomplete CRS (3-year OS of 0–26%, median OS of 13–24 months), despite giving intensive perioperative treatment including systemic chemotherapy, hyperthermic intraperitoneal chemotherapy (HIPEC) and whole abdomino-pelvic radiotherapy (WAP-RT).

Surgeons should nevertheless always balance the postoperative quality of life with the potential resection required to achieve a complete CRS. This anticipation of postoperative mutilation (bulky disease often located in the pelvis) and reduction of quality of life (linked to potential visceral and nervous resection) must be discussed with the patient preoperatively. The real challenge for the surgeon is to assess preoperatively the possibility for a complete CRS as cure cannot be achieved with chemotherapy alone or after incomplete surgery and also a survival benefit of incomplete resection has not yet been demonstrated. Optimal treatment ideally requires a team of medical specialists having expertise in peritoneal cancer surgery (and HIPEC). Complications may be expected in 16–25% of patients (deep abscess, anastomotic fistula, haemoperitoneum…). Nevertheless, in experienced centers, severe morbidity after complete CRS does not prevent the realization of a postoperative adjuvant treatment if required and should not limit surgical resection. Lymph nodes invasion is common in DSRCT (29–50%). Not knowing the origin of the disease, surgeons often experience difficulties for identifying the route of lymphatic drainage and for doing a complete lymph node resection, with lymph nodes recurrence being a frequent pattern of failure. In consequence, obviously completely resectable invaded lymph node should be resected but we do not know today if a systematic sampling is beneficial. This is one of the many remaining questions about surgery in DSRCT like the benefit can we expect from surgical debulking (i.e. incomplete CRS) in patients with an unresectable peritoneal disease or when extra-abdominal metastasis are present. Even if not associated with any survival benefit, it may prevent local complication or symptoms related to the disease's bulk. The role for complete CRS in patients with (resectable) extra-peritoneal metastases or justifying a mutilating pelvic surgery in young adults considering the poor prognosis of both situations are major surgical question to be answered in the future.

4.3.1.2 Radiation Therapy

Radiation therapy has commonly been used in all sarcomas for palliation or to increase disease-free survival. In DSRCT, with a local failure rate of 70–90% after complete surgery alone in DSRCT, all available locoregional treatments may be used to prevent local recurrences. Considering the sensitivity of Ewing-type sarcomas to radiation therapy, experiment on patients with DSRCT receiving since 1996 a conventional two-dimensional whole abdomino-pelvic radiotherapy (WAP-RT) at the dose of 30 Gy (plus boosts to sites of residual disease) at the Memorial Sloan Kettering Cancer Center demonstrated an improved local control but were also associated with major gastrointestinal and hematologic toxicities. These complications were majorly diminished using intensity-modulated radiotherapy and since those early days, many studies confirmed the benefit of postoperative WAP-RT to prevent locoregional relapse, with peritoneal recurrence rate after complete CRS of respectively 47% and 92% with/without WAP-RT. These finding are intuitively understandable considering the proportion of patients having peritoneal metastases and the risk of residual microscopic disease after complete macroscopic

CRS. Despite the safer methods to deliver WAP-RT, recent concern highlighted that the toxicity of WAP-RT could outweigh its putative benefits. A recent study suggested that systematic WAP-RT in chemoresponsive patients who underwent CRS did not improve OS. It may be possible WAP-RT only delay peritoneal recurrence and but still provided value by controlling symptoms and preserving quality of life. Those critical points must be balanced by the potential side effects, cost, and time required for radiation administration, and should be preferably assessed in any future trial implementing WAP-RT for DSRCT. No comparative study is available.

4.3.1.3 Intraperitoneal Chemotherapy

CRS plus HIPEC has been recognized as the standard of care for treating patients with peritoneal carcinomatosis of different cancer origin. Even if striking differences remain among treatment protocols, basket studies suggested a benefit of HIPEC in patients with peritoneal metastases of rare cancer origin, including DSRCT. A single retrospective study confirmed this benefit in terms of better local control using a combination of intraperitoneal cisplatin and doxorubicin. Unfortunately and considering the 43 patients with DSRCT reported worldwide (in 2017) having received intraperitoneal chemotherapy, these results failed to be confirmed in terms of overall survival benefit. In the largest series of patients treated for a DSRCT with complete CRS plus HIPEC, the median overall and disease free survival were respectively 31 months and 9 months when they were respectively 37 months and 12 months in patients of our series who did not had HIPEC. Potential explanations for this lack of benefit are multiple. First, HIPEC modalities are very heterogeneous and numerous without clearly identified best regimen or being potentially ineffective in mesenchymal tumors. PCI, a major prognostic factor, was in all series significantly higher in the HIPEC group and this could also have influenced the results. Although it would be very seducing to try to eliminate micrometastatic cells left behind after of surgery without true comparative study and stronger data, we must remain cautious before making any conclusion and have to consider the matter open to discussion. Adding HIPEC is surely responsible for higher morbidity whatever its indication and this was confirmed in DSRCT with a severe postoperative morbidity of 40% after HIPEC compared to 10% without HIPEC. This point is critical because with such a high rate of local failure, all hopes are intrusted in adding all potential solution. Some teams with this idea combined surgery, HIPEC and WAP-RT. The number of patients is too low and many fear a theoretical risk of cumulative late abdominal toxicity if the patient outlives his/her disease. In the only available retrospective study on eight patients out of whom 7 had HIPEC before 30 Gy whole abdominopelvic intensity-modulated radiation therapy (WAP-IMRT) postoperatively, no patient had developed grade 3 or 4 toxicity after a median follow-up of 15 months. To conclude we find no clear benefit of adding HIPEC in the literature, and currently we cannot recommend it to be systematically performed until further prospective data are available.

4.3.2 Systemic Treatment

4.3.2.1 Cytotoxic Chemotherapy

Chemotherapy has proved its value in Ewing sarcoma family to decrease the tumour bulk, to make surgery easier or to increase overall survival in palliative setting. In DSRCT, the situation is more complex because most patients have distant metastases (i.e. advanced-stage disease) at diagnosis, for which the outcome is dismal whatever the treatments as in any other cancer. Since all patients with DSRCT should be considered from the start metastatic, an induction chemotherapy should be the standard procedure. Nevertheless, there is a lack of consensus and choice of chemotherapy regimen rely today more on institutional practice rather than evidence based medicine. Treatment either includes chemotherapy extrapolated from Ewing sarcoma regimen, due to the similarities observed in genomics, histology, age, and sex ratio (high-dose cyclophosphamide, doxorubicin, and vincristine alternating with ifosfamide and etoposide, VDC/IE (vincristine, doxorubicin, cyclophosphamide/ifosfamide, etoposide), irinotecan/temozolomide, VAI (vincristine, doxorubicin, ifosfamide)) or chemotherapy used in soft tissue sarcoma (combination of doxorubicin and ifosfamide). All Ewing sarcoma s are remarkably chemosensitive but no regimen proved superior to another in DSRCT. Even if earlier studies reported lesser response rates using doxorubicin-based chemotherapy, no major differences in response rates between various regimens are found in the latest series. Expected objective response rate is high in DSRCT (between 65% and 80%) and progression uncommon (around 10%). Increasing the burden of chemotherapy has never proven to add any survival benefit in DSRCT. On the other hand, minimizing the number of agents for tailoring subsequent regimens based on response to the initial therapy, and lowering the chemotherapy-induced toxicity is therefore seducing. This is very important, especially in adult patients in whom systemic treatments are less well tolerated than in their younger counterparts. Without clearly proven survival benefit, induction chemotherapy in patients with DSRCT could aim preoperatively to decrease the tumor bulk, and thereby select patients with favorable tumor behavior. The regimen may be adapted to the needs of the surgeon to make the disease resectable, with the idea of keeping available drugs in case of subsequent relapse and avoiding chemotherapy-related undue toxicity. To support this idea a handful of patients with DSRCT even underwent autologous stem cell transplant (ASCT) after high dose chemotherapy with limited benefit. Although perioperative chemotherapy has proven its prognostic value in Ewing tumors family, the benefit of adjuvant chemotherapy is still unknown in DSRCT. Adjuvant strategy based on post-treatment percentage of necrosis was reported with better outcome and may be an interesting alternative to develop. Despite being sensitive to alkylating agents, the absence of complete pathological response in DSRCT highlights the need for complete CRS to increase survival rates. CRS after induction chemotherapy is associated with better median overall survival (34 vs. 14 months) than those treated with systemic chemotherapy only. Nevertheless, patients progressing under

induction chemotherapy should not be eligible for surgery. Progressive disease (PD) under chemotherapy remains a strong surrogate for tumor aggressiveness. In all series, patient with PD under induction chemotherapy who anyway underwent "rescue" surgery experienced dramatic disease relapse in the peritoneum, liver, lung and lymph nodes less than 6 months after surgery despite aggressive postoperative treatments. The aim of preoperative chemotherapy in DSRCT is to decrease the tumor bulk for facilitating complete CRS and select favorable tumor biology. As the regimen, the timing of induction chemotherapy is unknown. Most teams propose surgery after 3–6 months of treatment without evidence based data. There is no certainty on the best treatment in second-line therapy and beyond, temozolomide/irinotecan, cyclophosphamide/topotecan, and high-dose ifosfamide, which have proven clinical activity in chemotherapy-resistant Ewing type sarcoma. Less common salvage regimens included cyclophosphamide/vinorelbine, gemcitabine/docetaxel, and dacarbazine. Eribulin has never been tested in Ewing family sarcoma but since microtubule inhibition seems historically in this cancer subtype, further may be warranted. Some cytotoxic agents such as trabectedin, gemcitabine, irinotecan were tested with globally disappointing results. Despite very aggressive front-line systemic treatments, more than 90% of patients died of disease recurrence, suggesting that we failed to eradicate hidden tumor cells and/or failed to reach sanctuaries.

4.3.2.2 Targeted Therapies

No targeted therapy is specifically available for DSRCT. DSRCT is characterized by a recurrent chromosomal translocation: t(11;22)(p13;q12) fusing the ESWR1 gene to the WT1 gene. The resulting chimera encodes a novel aberrant transcription factor (TF) constituted of the potent transcriptional activation domain of EWSR1 and the DNA-binding domain of WT1. We suspect this alteration to be responsible of the transformation of mesenchymal stem cells and being the unique oncogenic driver of this disease. Targeting TFs is particularly challenging, as: (1) they regulate a plethora of downstream transcriptional programs whose isolated inhibition is insufficient, (2) they lack ligand-binding domain or catalytic pocket that can be targeted, (3) their most well-known "interactor" is the cognate DNA-consensus sequence which interacts with a protein surface that is too large to be druggable. Alternative strategies, aiming at preventing the expression of TF, increasing its degradation or interfering with its essential co-factors, could therefore be explored. With very few translational researches focusing on DSRCT, most treatment data are coming from small retrospective series using off-labeled drugs with in the end a very low level of evidence. The upregulation of PDGFA in DSRCT led to the evaluation of Imatinib with dismal results. Preclinical studies have shown that VEGFR-2 and VEGFA are overexpressed in DSRCT and sunitinib was tested, but without striking effect. Although neoangiogenesis pathway seems to have an important role in DSRCT pathogenesis, bevacizumab has demonstrated limited activity in DSRCT. On the other hand, pazopanib, a multikinase inhibitor targeting the VEGF

receptors, seems to exert significant clinical activity. In a DSRCT cell line, the mTOR inhibitors (rapamycin or temsirolimus) induce apoptosis but this effect was not translated in clinical activity. Insulin-like growth factor 1–receptor (IGF-1R) inhibition has been seen to mitigate the mTOR activation and its additive antitumor activity in combination with mTOR inhibitors demonstrated interesting clinical activity in patients with Ewing family sarcomas, including DSRCT. Androgen receptors are highly expressed in DSRCT but with short responses in clinical setting. Nevertheless, considering the male/female ratio in this disease, this pathway deserves to be investigated. To conclude: no targeted therapy has demonstrated yet a striking benefit and we need more tumor biomarker evaluations in prospective trials and whole genome sequencing and immune-profiling of DSRCT samples are urgently required in order to try to identify potential targets of transcriptional dysregulation.

4.3.2.3 Immunotherapy

In an era where immunotherapy plays a prominent role in treatment for many different cancer types, the use immunotherapies in DSRCT has not been reported yet in the literature and we have no scientific data to support its use.

4.4 Survival and Decision Scheme

Without any comparative data, treatment in DSRCT is based on prognostic factors to identify the best decision scheme. However, despite aggressive strategy, most patients eventually relapse and die from their disease. The median overall survival (OS) after DSRCT diagnosis ranges between 19 and 32 months and the 3-year OS ranges between 27% and 48%. Surgery is one of the main components in treating DSRCT but the challenge is to accurately select the eligible patient who may benefit the most out of this morbid procedure. Currently, the selection is based on: (1) response to induction chemotherapy (adequately evaluated on CT scanner) and (2) feasibility of a complete CRS. This last criteria is more than just being technical because it encompass other factors associated with prognosis (absence of extra-abdominal disease, high PCI, diffuse hepatic disease although resectable) or quality of life (resectable but mutilating surgery). This selection is the most difficult task for the surgeon because without surgery, median OS is 19 months, after incomplete surgery, median OS is 24 months and after complete surgery, median OS is 36 months. Despite interesting retrospective data, the value of hyperthemic intraperitoneal chemotherapy (HIPEC) and whole abdomino-pelvic radiotherapy (WAP-RT) remain undemonstrated and further studies are required.

Nevertheless, our ability to eradicate the disease despite very aggressive treatments (systemic chemotherapy, surgery, HIPEC and/or WAP-RT) is limited as recurrence occurs in of 77–90% of patients (5-years disease free survival of 12%).

The pattern of failure after complete surgery is informative because after complete CRS, 69–88% experience at some point during their evolution a peritoneal recurrence that occurred (after a medial delay of 11–13 month).Other ne recurrence sites include lymph nodes, lung, liver and bone. Considering our inability to eradicate th ereisdual disease, a prolonged adjuvant treatment might be given as a preventive measure. The potential candidates for such a treatment could be either mTOR inhibitor, multikinase inhibitor targeting the VEGF receptors and androgen receptors inhibitor that have all been tested in metastatic situation with encouraging results and that have side effect that might be considerate tolerable for a long lasting adjuvant setting. These treatments have never been tested in this indication and should be evaluated in a prospective trial. Few long survivors have been reported across all series of DSRCT, but in the absence of a large population with enough follow-up, we have no clear information on these patients and potentially on the reasons why their disease never recurred. In nation-wide survey, patients with a prolonged survival after DSRCT diagnosis were analyzed to identify potential factors associated with a cure. In univariate analysis, predictive factor of being free of disease at 5 years were female sex, median PCI below 12, MD Anderson stage 1, completeness of CRS and postoperative WAP-RT. The existence of extraperitoneal metastases did not reach statistical significance if resection was complete and hyperthemic intraperitoneal chemotherapy (HIPEC) did not increase statistically the rate of cure. Among the 25 patients who received radiotherapy after complete surgery, 6 were still disease-free after more than 5 years. Cure defined as being disease-free at 5 years is therefore possible in 5% of patients. This rate is strictly similar to the one reported in other patients with metastatic soft-tissue sarcomas.

4.5 Conclusions

DSRCT is a complex disease with a dreadful prognosis and due to its rarity; the optimal treatment still needs to be defined. Yet, cure is possible in 5% of patients. The best available treatment should combine induction chemotherapy and complete CRS. Postoperative WAP-RT, postoperative chemotherapy may be discussed. The value of adding HIPEC remains largely unknown and considering the absence of durable response even after complete CRS, the question of a long term consolidation treatment may be addressed. Despite aggressive treatment, recurrence and progression is common and targeted treatments are urgently needed. To increase our knowledge on this rare disease, collaboration at an international level with centralized prospective database is needed. Nevertheless, clinical database come to the limits of what they can bring and that the next revolution in treating DSRCT will come from biological research. The incorporation of molecular information to further select targeted therapy is probably the key to improve survival in the future. Prospective, randomized, multicenter cooperative trials will be required to evaluate those local-control modalities and to advance novel biologically targeted therapies.

Further Reading

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Chapter 5
Solitary Fibrous Tumours

C. Bouvier and S. Salas

5.1 Definition

Solitary fibrous tumors (SFT) are unusual ubiquitous soft tissue tumors categorized as having intermediate biological potential with a low risk of metastasis. Although most cases are considered as benign, they may behave unpredictably. About 10% behave aggressively with local and distant recurrence many years after primary resection. These rare tumors, which are presumed to be of fibroblastic differentiation, usually affect adults and can occur at any site. SFT belong to the prognosis category "intermediate" of the WHO classification of Soft Tissue Tumours since even most are benign some can behave unpredictably with recurrence and metastasis [1].

5.2 Epidemiology, Site of Insolvent and Clinical Features

SFT occur most often in middle-aged adult aged 20–70 years, with cases in children and adolescents being rare. The median age was 58.5 (range 15.6–87.4) in a multicenter cohort from the French Sarcoma Group (FSG) database. Two thirds of patients were female. Solitary Fibrous Tumours are unusual mesenchymal neoplasm initially described in pleura, however SFT may be found at any location. The main locations are soft tissue, thorax, abdominal cavity, retroperitoneum, meninges and viscera. Up to 40% are found in subcutaneous tissue, while other arise in deep soft tissue. Most tumours are well-delineated slow growing mass while malignant tumours are more infiltrative. Large tumours may give rise to compression

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symptoms. Rarely, large SFTs tumors may be responsible of paraneoplastic syndrome such as hypoglycemia due to IGF2 secretion. The size is variable: 1–25 cm with a median of 6 cm.

5.3 Pathological and Genetic Diagnosis

Macroscopically these tumours are well defined sometimes with a peripheric capsule. On section they are a usually white and fascicular mass. Necrosis may be present. On microscopy typical SFT show a patternless architecture with a combination of hypocellular and hypercellular areas. In the hypocellular areas the stroma is collagenic "keloidal" more rarely myxoid. There are ovoid or spindle bland cells with scant cytoplasm. The hypercellular areas contained sheets of cells with thin-walled branching haemangiopericytoma-like vessels. By the past, if these areas were found isolated the tumours were called haemangiopericytoma. It has disappeared from the WHO classification of soft tissue tumours since it is now established that SFT and haemangiopericytomas are the same spectrum of tumours. Mitoses are found in variable number. Necrosis is seldom present usually in hypercellular areas. Haemorraegic areas are also found. Morphological variants are described. Giant cell angiofibromas correspond to SFT with giant multinucleate stromal cell and pseudovascular spaces. When SFT contain a prominent adipocytic component they are called Fat-forming SFT. The histological differential diagnoses encompass benign tumours such as myopericytoma, myofibromatosis and malignant tumours such as synovialosarcoma, mesenchymal chondrosarcoma and infantile fibrosarcoma. The final diagnosis is achieved with immunohistochemical study. CD34 is usually widely expressed but with some heterogeneity. Other non specific markers are variably expressed: CD99, bcl2… Some markers such as ALDH1 and GRIA2 have emerged from transcriptomic studies and were useful until the discovery of specific genetics data: the *NAB2-STAT6* fusion. Today the diagnosis is made by typical histological features, specific immunohistochemical phenotype and or genetics data: the *NAB2-STAT6* fusion. In 2013, two different teams simultaneously reported a *NAB2-STAT6* fusion transcript in most SFTs whatever their localization [2, 3]. The discovery of *NAB2-STAT6* gene fusion by integrative sequencing was a big step forward in the characterization of SFTs. Remarkably, the *NAB2-STAT6* fusion eventually leads to nuclear translocation of the C-terminal portion of STAT6, which can then be detected using immunohistochemistry [4, 5]. STAT6 immunohistochemistry has been shown to provide excellent sensitivity and specificity for routine histological diagnosis [6]. Several studies have shown its high sensitivity and specificity because only few other soft tissue tumours could expressed it. Doyle et al. [7] and De Micco et al. [8] recently reported the expression of moderate-to-strong STAT6 in up to 12% of dedifferentiated liposarcomas, and determined that STAT6 expression was due to gene locus inclusion in the 12q13~15 amplicon characteristic of this tumor. In that case elevated expression is likely to be due to amplification and subsequent overexpression of full-length STAT6. Intimal sarcomas also possess 12q15

amplification and thus may also express STAT6. Few pleomorphic sarcomas could also be positive in few cells.

5.4 Prognostic Factors

Few authors have searched for prognostic factors in large series of primary solitary fibrous tumors. These studies showed controversial issues when considering individual clinical or histological parameters. Most interesting is the association of clinical and pathological parameters. The largest series that had a rigorous statistical analysis was published by De Micco et al. [9], Pasquali et al. [10], Salas et al. [11], and Gholami et al. [12]. They all identified clinicopathological prognostic factors and some of them proposed a risk model assessment and a risk calculator.

Several studies have suggested that tumor size >10 cm is a prognostic factor of metastasis-free survival but tumor size was not predictive of poor prognosis in the cohort from the French Sarcoma Group (FSG) [11]. Recently in a series of 219 patients size greater than 8 cm was associated with local and distant recurrence and death specific disease in multivariate analysis [12].

Age is a clinical parameter with controversial prognostic value and several cut off are found in the literature. We have found that age under 60 years old was statistically associated with longer survival and a low MRI in multivariate analysis. In contrast, age under 60 years old was a negative prognostic factor for local recurrence. The identification of different *NAB2-STAT6* gene fusion transcripts according to different clinical settings emphasized the impact of age, some fusion variants being more common in older patients. For example, *NAB2* exon *4-STAT6* exon 3 fusion correlated with classic fibrous morphology, older age, pleural localization and low mitotic activity, while *NAB2* exon6-*STAT6* exon16/17 was found in much younger patients [13].

The anatomic site of primary tumors has also been reported to predict outcome. In our series, visceral location was pejorative for local recurrence while tumors in limbs behaved more aggressively with a significant difference in metastatic recurrence incidence in multivariate analysis. Gholami et al. [12] reported that location in chest or abdominal/retroperitoneal cavity significantly impacted the death specific disease.

The most studied histological parameters are cellularity, mitotic index and necrosis. The WHO classification of soft tissue tumors recognizes a malignant category of SFT defined by “hypercellularity, variable atypias” combined with mitotic count >4/10 high-power fields, necrosis and/or infiltrative margins.

Hypercellularity is a subjective parameter with no precise definition.

Mitotic activity seems the best histological prognostic factor for SFTs whatever their localization. The prognostic value of mitotic count was reported in most series with a cut-off of four or more mitoses or strictly more than four mitoses per 10 high power fields. We found that it was the only histopathological parameter with a prognostic value for overall survival in our series. This raises the issue of a separate

group of patients with high mitotic score who could potentially benefit from more aggressive therapeutic strategies. Mitotic count should therefore be included in any standardized pathological report. However recently, Gholami et al. [12] did not find prognostic value of the "histological malignant" component defined by 4 or more mitoses for 10 high power fields.

The prognostic value of necrosis is controversial. Gold et al. [14] found that it had a prognostic value in univariate analysis only for time to recurrence and that it was not a compulsory parameter for malignancy. De Micco et al. [15] and Salas et al. [11] found that it was a prognostic factor of MRI and OS in univariate analysis. Tapias et al. [16] used the item necrosis or hemorrhage in their scoring system for pleural SFT recurrence.

Recently, an individual risk calculator was proposed by Salas et al. [11] to quantify the risk of both local and metastatic recurrence. The parameters that influenced local recurrence were: age <60 years, visceral location and the use of radiotherapy. Metastatic recurrence was dependent of age, limb location and mitotic index >4/10. This survival calculator could become standard practice in SFTs to individualize treatment based on the clinical situation.

De Micco et al. [8] also recently proposed a refinement of their risk stratification model adding necrosis to the previous parameters: age, tumour size, mitotic count.

5.5 Outcome

The overall survival rate at 10 years was about 75% for patients without metastasis at the time of diagnosis. OS rates decreased to 50% at 20 years. This confirms the poor prognosis of these tumors in the long term and the need for protracted follow-up. Otherwise, LRI and MRI rates increased between 10 and 20 years so relapses were delayed. The LRI rates at 10 and 20 years were 19.2% and 38.6%, respectively in our series [11]. Gholami et al. [12] reported metastatic recurrences as late as 16 years after the initial presentation even in patients with tumours initially classify as histological benign. This suggests that long-term monitoring is useful and that complementary therapies are probably necessary for some patients, although their benefit in the first years is not easy to demonstrate.

5.6 Treatment

Surgery is the mainstay of treatment. De Micco et al. [15] and Salas et al. [11] found no significant association between positive margins and eventual metastasis or local recurrence but in contrast to Gold et al. [14]. However, surgical margins have prognostic value in many other histologic types of soft tissue sarcomas. These controversial findings may be explained partially by the difficulty to evaluate surgical margins in retrospective studies. The use of radiotherapy in these tumors is

controversial. van Houdt et al. [17] found no significant beneficial effects of adjuvant radiotherapy on LRI or MRI in 19 patients. Recently, Bishop et al. [18] reported that treatment of soft tissue SFT using combined surgery and radiotherapy in 31 patients (preoperative radiotherapy in 14 patients and postoperative radiotherapy in 17 patients) resulted in excellent local control with no local relapse at the end of follow-up. Salas et al. [11] showed that postoperative radiotherapy was a good prognostic factor of LRI. These results and those of Bishop et al. [18] suggest that radiotherapy should be part of the therapeutic strategy, although only a prospective randomized trial taking account of prognostic factors could confirm the beneficial effect of radiotherapy in SFT. In the meantime, use of an individual risk calculator to quantify the risk of local recurrence could help in making a decision about whether or not the patient should be treated with additional radiotherapy. Systemic treatments could be used in case of metastasis as in other mesenchymal tumors. Cytotoxic chemotherapy has limited activity for patients with advanced disease, with small case series and retrospective studies suggesting marginal benefit [19–22]. Several studies have suggested a significant activity of antiangiogenic drugs in the treatment of advanced solitary fibrous tumours, and the clinical use of Choi criteria as more appropriate indicators of response in patients with sarcoma than traditional RECIST criteria [23]. In a study of bevacizumab in combination with temozolomide in 14 patients with advanced hemangiopericytoma or solitary fibrous tumours, 11 (79%) patients achieved a partial response according to Choi criteria, with a median progression-free survival of 9·7 months [24]. Among 31 evaluable patients with solitary fibrous tumours treated with sunitinib, two (6%) had a partial response according to RECIST, but 14 (48%) had a partial response according to Choi criteria [25]. Through an international collaboration between Italian, French, and Spanish sarcoma groups, the anti-angiogenic agent pazopanib was investigated for the treatment of advanced malignant and dedifferentiated solitary fibrous tumours in a phase II study. Median progression-free survival was 5·6 months (95% CI 4·51–6·62), 40% of patients achieving 6-month progression-free survival, and 73% (58–88) achieving 2-year overall survival [26]. Such promising efficacy was also confirmed in patients typical solitary fibrous tumour at the time of disease onset [27]. Altogether, these results suggest that antiangiogenic therapies—specifically pazopanib—for the treatment of malignant solitary fibrous tumours should be considered a viable and reasonable approach.

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Chapter 6
Alveolar Soft Part Sarcoma

S. N. Dumont, D. Orbach, A. Coulomb-L'herminé, and Y. M. Robin

6.1 Epidemiology

ASPS is a rare entity representing 0.5–1% among soft tissue sarcomas. Expert centers receive an average of 1–2 new cases a year and about 40 a year in France, 57 between 2010 and 2014 in the United States, according to the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. It occurs mainly in adolescent and young adults between 15 and 40 years of age. Prevalence is greater in women than men and it occurs in adult patients for about 60% of cases [1]. Indolent but still lethal, this disease survival is a dismal of 77% at 2 years, 60% at 5 years, 38% at 10 years and 15% at 20 years. For localized disease, survival at 5 years is 71% but 20% for metastatic disease [2].

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6.2 Clinical Features

At diagnosis, patient with ASPS describes a slow-growing mass in the extremities. It is usually painless and highly vascular, sometimes pulsatile. Due to the scarcity of symptoms, diagnosis is often delayed which explains that 80% patients have metastatic disease at diagnosis.

In the adults, the most frequently involved locations of ASPS are the deep soft tissue of the lower extremities, especially the thigh and buttock [2]. This stands in contrast to the pediatric population where the tumor clearly has a predilection for the head and neck, and in particular the tongue and orbit [3]. ASPS has also been described as a rare primary lesion of the calvarium [4], and of the pleura [5]. In the viscera, occurrences have been reported in such diverse anatomic sites as liver [6], lung [7], gastro-intestinal tract [8], breast [9], uterine corpus [10] and cervix [11], and the urinary bladder [12]. Deep soft tissue tumors may measure more than 10 cm. Head and neck tumors are generally much smaller.

Metastasis sites are predominantly lung, bone and, unlike other sarcomas, brain which are extremely frequent. Metastases can be delayed, sometimes 15 years after initial diagnosis [2].

6.3 Imaging

Ultrasounds are sometimes misleading as ASPS being hypervascular, it may mimic an arteriovenous malformation. Magnetic resonance imaging (MRI) is the best technic to refine the diagnosis of a slow growing bulging mass, by an expert radiologist. ASPS will exhibit a high T1 and T2 signal. Chest CT scan and a brain MRI is part of the mandatory baseline imaging to assess metastatic status (Fig. 6.1).

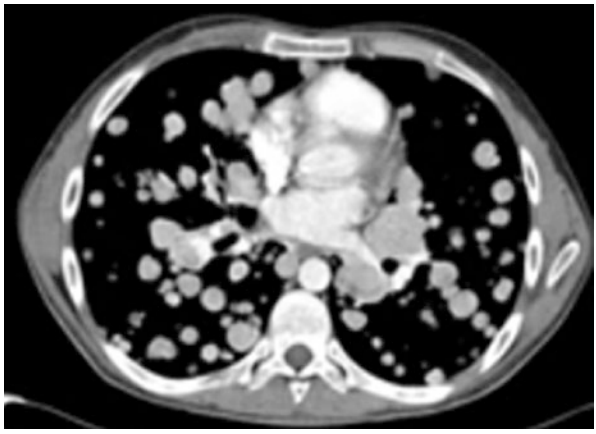

Fig. 6.1 Diffuse bilateral lung metastases on a chest CT-scan in a 22 year-old young lady with a ASPS originating from the left thigh

6.4 Pathology

6.4.1 Definition, Historical Basis and Broad Considerations

ASPS is of uncertain cellular lineage, consisting of individualized groups of large rounded cells with characteristic crystalloids, set in a finely capillarized stromal background, and exhibiting the recurrent unbalanced translocation der(17)t(X;17)(p11;q25) [1]. The observed female predominance is theoretically explained by the fact that statistically the risk of a translocation involving the X chromosome present in two copies is greater in women [13]. Neither the cytophylectic nature of the tumor nor its direction of differentiation are established although differentiation patterns currently form the basis of the histopathological classifications of sarcomas [14].

Historically one of the longstanding prevailing hypotheses following the initial description of the tumor by Christopherson, Foote and Stewart [15] concerned the controversial issue of its myogenous phenotype, now abandoned, which for some times had fueled the still unsettled question of its histogenesis. Masson had first classified this tumor among muscle lesions [16]. Afterwards, much data followed, which originally seemed to corroborate the idea of striated muscle differentiation based on three main factors. One of these was the observed cytoplasmic expression of muscle-associated proteins (among which desmin, B-enolase, muscle-specific actin, MM isozyme of creatine kinase) [17–25] and nuclear expression of the skeletal muscle-specific regulatory protein MyoD1 using immunochemistry and immunofluorescent techniques [23]. This ultimately proved unsustainable for the following reasons. Among the muscle-related proteins, desmin for example, is not considered a specific marker of skeletal muscle tissue differentiation and can be found expressed in a number of very different lesions such as smooth muscle proliferations, rhabdoid tumors, Ewing sarcoma or neuroblastoma [26]. As for the nucleophosphoproteins MyoD1 and myogenin, the lack of convincing robust confirmatory data in subsequent reported cases rendered irrelevant the formerly observed putative positivity. Immunohistochemical nuclear expression was undetected in 12 cases studied by Wang et al. [27] and in 19 other cases described by Gomez et al. [28]. Moreover, these authors noted spurious granular cytoplasmic staining presumably resulting from non-specific cross reactions with other functionally unrelated antigens. In these reports Western blotting failed to highlight the expected corresponding 45-kd band of MyoD1. Also, MyoD1 transcript has not been picked up by Northern blot analysis [20]. Furthermore, no ultrastructural evidence of myofilaments has been unearthed in alveolar soft part sarcoma [27, 29]. Miettinen and Ekfors, though favoring the myogenous theory in one 1989 publication, were not outright affirmative, precisely because of the absence of characteristic filaments in electron microscopy [24]. Another main factor apparently in favor of muscle differentiation was a proposed ultrastructure of the crystalloids supposedly composed of Z-band tropomyosine B, similar to that of rod structures seen in nemaline myopathy and rhabdomyoma [30]. This was refuted in the light of new data demonstrating the absence of tropomyosin [31]. Thirdly, some later investigations in gene expression profiling seemed

to lean again toward the concept of muscle cell origin with the identification of differentially expressed genes [32, 33]. But once more, further studies failed to support these findings [34].

Quite recently, in the continual search for a cellular progenitor in ASPS, one report of expression profiling results suggested a neural differentiation in line with the enhanced expression of the paired box transcription factor PAX6, a putative tumor suppressor which plays a significant role in the activation of neural genes [35, 36]. Curiously a neural crest origin had been speculated as far back as 1982 [37].

In other former attempts for classification, ASPS was described by DeSchryver-Kecskemeti et al. as "malignant angioreninoma" reminiscent of juxtaglomerular cells following the detection of positive staining with fluorescein-tagged antirenin antibodies in tumor cell [38]. However, arterial hypertension was not a clinical feature in cases reviewed and biochemical studies by others authors revealed neither active nor inactive tumor renin secretion [31]. ASPS has also been diversely referred to as "malignant myoblastoma", "granular cell myoblastoma", "malignant granular cell myoblastoma" [39–41] or as "malignant tumor of the non-chromaffin paraganglia" [42], terms which are all universally considered inappropriate.

Other soft tissue malignancies such as synovial sarcomas, epithelioid sarcomas or malignant rhabdoid tumors mirror ASPS in as much as they have no known benign counterparts, a singular factor which can perhaps be linked one way or another to the absence of a specific line of differentiation.

6.4.2 Gross Morphology

When excised, ASPS has a soft consistency with uncapsulated borders. The cut surface has a white to yellow-brownish color tinged with hemorrhagic spilling or central necrosis in large tumors (Fig. 6.2a).

6.4.3 Light Microscopy

ASPS bears a distinctive morphological structure easily recognizable in a majority of cases. It is composed of large nest-forming epithelioid round or polygonal cells with an alveolar and sometimes dyscohesive arrangement grounded in a delicately vascularized stroma where lympho-vascular invasions are common (Fig. 6.2a–c). Cytological features are also typical: individual monomorphic tumor cells showing an abundant granular eosinophilic or clear glycogen-rich cytoplasm with neatly outlined borders and an eccentric vesicular nucleus containing a prominent central nucleolus (Fig. 6.2d, e). Less frequently, sheets of contiguous individual or small nest of cells displaying an overall solid appearance are seen (Fig. 6.2f, g). This aspect is mainly found in children. Multinucleation is common (Fig. 6.2h). No cross striations are visible. Mitoses are scant and necrosis rather rare. Some tumors

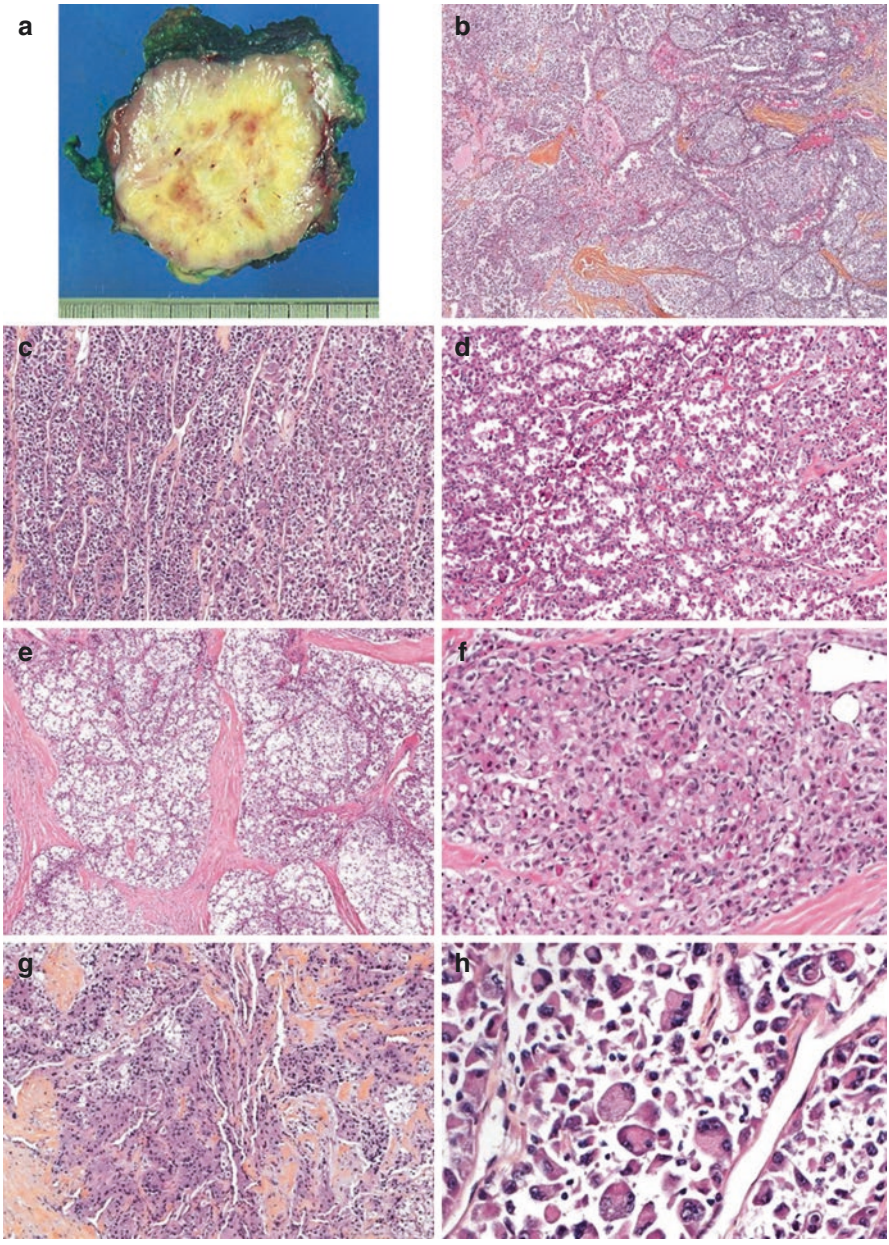

Fig. 6.2 (**a**) surgical resection shows a deep unencapsulated circumscribed 5 cm mass involving skeletal muscle with a gray-tan colour and central necrosis, (**b**) On low power HES staining, ASPS shows the typical alveolar architecture, (**c**) Delicately disposed thin-walled capillaries separate nests of ASPS cells on HES, (**d**) ASPS Cells o HES display an abundant eosinophilic granular cytoplasm, (**e**) Clear cell changes in ASPS on HES, (**f**) Solid variant architecture of ASPS, (**g**) A solid and hyalinized section of ASPS reminiscent of granular cell tumour, (**h**) Multinucleation is a common feature of ASPS

differ in appearance from this classic description and show other less characteristic aspects such as nuclear pseudo-inclusions, myxoid and cystic changes, reactive vascular proliferation, hyalinization, focal calcification with psammoma bodies and lymphocytic infiltrate [1, 2, 42–50]. Other rare features may raise diagnostic concerns: numerous mitotic figures, polymorphism or spindling of tumor cells, coagulative necrosis or xanthomatous changes [9]. Surgical resection of lung metastasis shows a similar histological pattern with vascular involvement (Fig. 6.2e).

Special histochemical stains such as alcian blue, trichrome or periodic acid-Schiff with diastase can identify rod-like or rhomboid diastase-resistant membrane-bound intracytoplasmic crystalline formations originally described by Masson [16] and intrinsically associated with the lesion (Fig. 6.2b). Investigations by Ladanyi et al. conclude that these crystals are in fact complexes of monocarboxylate transporter 1 (MCT1) interacting with its chaperone protein CD147 [51]. These characteristic findings are not ubiquitous and their detection can eventually require extensive scrutiny in different sections of the tumor. In some cases only a granular–type substance is noted instead of definitely formed crystals, representing presumably a pre-crystalline variant of the MCTI-CD147 complex [51].

6.4.4 Ultrastructure

Electron microscopy, largely supplanted by immunohistochemistry for the great majority of tumors since its expansion in the 1980s, is not a routine diagnostic asset. Observations show that ASPS cells are poor in desmosomes and rest on incomplete basement membranes in contact with capillaries [43, 47]. The cytoplasm contains usually sparse endoplasmic reticulum, numerous mitochondria and an extensively developed golgi apparatus [43]. The latter is associated with the partially or pre-crystallized electron-dense transitory-type granules mentioned above measuring 120 nm along with the crystalloids bearing a periodicity of 100 Å, both of which are membrane-bound [31, 43, 47].

6.4.5 Immunohistochemistry

Immunostaining is in most cases of limited diagnostic interest. From our perspective only three markers appear to be important for the diagnosis. Transcription factor TFE3 shows nuclear positivity in line with the rearrangement of the gene fusion ASPL-TFE3 (Fig. 6.3). TFE3 immunoreactivity is not entirely specific to ASPS as it can also be observed in a number of other tumors such as a subset of PEComas [52], malignant melanoma, granular cell tumor and above all pediatric renal cell carcinoma [53].

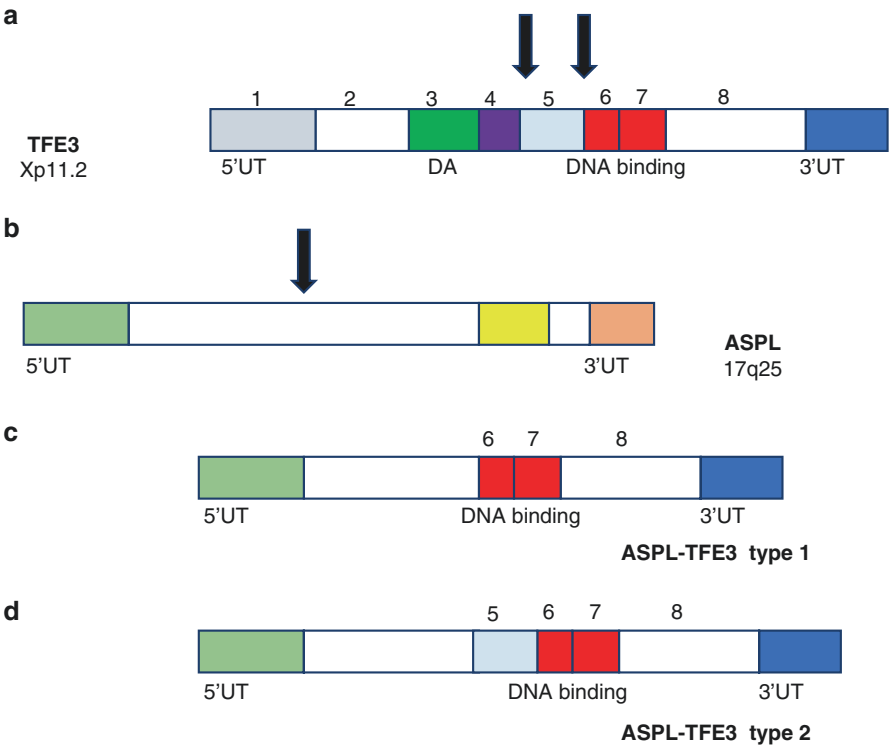

Fig. 6.3 Schematic diagram of normal TFE3 (**a**) and ASPL (**b**) genes and type 1 (**c**) and type 2 (**d**) fusions defining ASPS. Arrows indicate breakpoints

Sensitivity on the other hand is quite high, on the order of 92% in ASPS, yet staining can be weak and even absent in some cases, particularly in inadequate pre-analytical sample preparations, which does not exclude the diagnosis [54].

Strong surface and cytoplasmic immunohistochemical labeling of CD147 may be, albeit to a lesser degree, of diagnostic utility knowing that positivity has also been reported in other tumors (granular cell tumor and clear cell renal cell carcinoma) [54]. CD147 (also known as EMMPRIN for extracellular matrix metalloproteinase inducer) is a member of the immunoglobulin superfamily and is known to be expressed by tumor cells stimulating adjacent fibroblasts to elaborate matrix metalloproteinases. As such, it would seem to favor tumor invasion and metastasis, thus representing a marker of poor prognosis. Its role as a potential therapeutic target is debated [54, 55].

The third marker worthy to be noted is cathepsine K, a protease whose expression is activated by the micropthalmia transcription factor (MITF) in osteoclasts. Cathepsine K immunostaining in ASPS is highly constant, cytoplasmic and diffuse. However it lacks specificity, being also expressed in melanoma, clear cell sarcoma, granular cell tumor and PEComa [56, 57].

Other immunoreactive markers with low significance in ASPS include desmin, actin (6–14), weak S-100 protein expression [21], NKIC3 [22], histiocytic marker CD68 KP1 [58] and also vimentine [24]. The latter reactivity is anecdotal as opposed to what is often noted in other mesenchymal or undifferentiated sarcomas where it is in general either intense or diffuse or both, and so of negligible diagnostic value in all these cases including ASPS. In the negative range of the panel, one finds nuclear myogenin and MyoD1 (although aberrant cytoplasmic reactivity may be detected as already underlined), the epithelial markers keratin and epithelial membrane antigen (EMA), the neuroendocrine markers chromogranin, synaptophysin or a number of neuropeptides, neurofilament and glial fibrillary acidic protein (GFAP) [24, 47, 50]. As is the rule for sarcomas in general, the eventual clinical utility of standard immune complementary immunohistochemical tests in ASPS is yet to be determined. As mentioned earlier, lymphocytic infiltrate is a rare event in this sarcoma. However, Goldberg et al. seem to have been able to identify PD-1 (programmed death-1) pathway activation with tumor cells showing immunoreactivity for PD-L1 (PD-ligand 1) and individual CD8+ tumor-infiltrating T cells expressing PD-1 [59]. This however needs to be confirmed with more extensive data.

6.4.6 Genetics

The defining molecular genetic feature of ASPS is unequivocally the recurrent non reciprocal translocation der(17)t(X;17)(p11;q25) and the resulting chimeric fusion gene and transcript. Because of its high specificity and sensitivity [54], it is considered as the gold standard of the tumor's classification. This translocation between the two involved chromosomes X and 17, was first identified, among other alterations (both structural and numerical), by karyotypic investigations [60] followed by the identification of the two breakpoints on Xp11.2 and 17q25 [61]. This paved the way for the characterization of the two corresponding genes [13], the ubiquitously expressed transcription factor TFE3 on Xp11.2 and a novel likewise widely expressed gene whose function is unknown, hitherto named ASPL/ASPSCR1 (alveolar soft part sarcoma locus/alveolar soft part sarcoma chromosomal region) on 17q25 (Fig. 6.3a, b). In the ASPL-TFE3 chimeric oncoprotein, the COOH-terminal sequences and the DNA binding domain of TFE3 are maintained but its N-terminal sequences are replaced by ASPL, disrupting innate TFE3 transcriptional activity. The oncoprotein acts as an aberrant transcription factor once localized to the nucleus.

Two reported cases show a reciprocal translocation, deviating from the common feature [13, 62]. Two mutually exclusive translocation variants have been identified although observations are too scant to conjecture any predictable differential clinical impact. The ASPL gene has a unique breakpoint whereas the TFE3 gene is variably exposed, with two possible breakpoints yielding two types of fusion. According to Ladanyi et al., in type 1 fusion the ASPL gene is joined in frame to the fourth

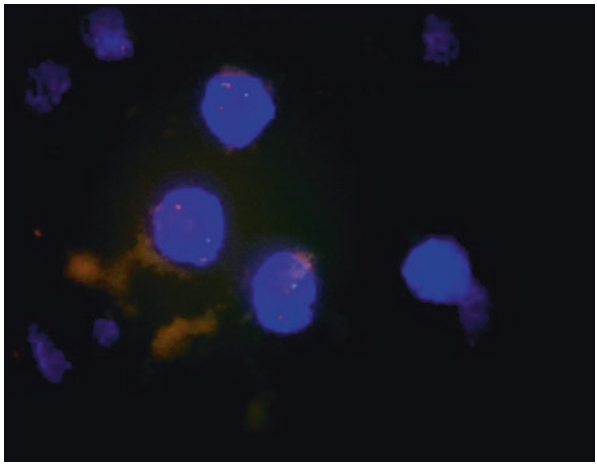

Fig. 6.4 Fluorescent in situ hybridization (FISH) using break apart probes targeting the TFE3 gene. Cells in upper left quadrant show rearrangement of the gene with a split between red and green signals

exon of TFE3 (excluding exon 3) and in type 2 with the third exon. However under the current reference sequence (GenBank NM_006521) which introduced a change in exon nomenclature (with no biological consequence) since Ladanyi's publication, in type 1 the truncated ASPL gene (exons 1–7) sequences directly with the sixth exon of TFE3 (excluding the fifth exon) and in type 2 with exon 5 [59, 63] (Fig. 6.3c, d).

In routine laboratory practice, the translocations are usually diagnosed by fluorescent in situ hybridization (FISH) using break-apart TFE3 gene target probes (Fig. 6.4). RT-PCR analysis (Reverse Transcription-polymerase chain reaction) designed for formalin fixed paraffin-embedded tissue is an alternative however [56, 63, 64] and has been even proposed as the most powerful diagnostic test for ASPS, being of greater sensitivity (100%) than anti-TFE3 immunostaining, provided that RNA extracted from paraffin-embedded material is of good quality and did not suffer degradation. It is further suggested that sensitivity is enhanced by the use of nested PCR presumably because of the increased number of cycles [54].

The molecular mechanisms driven by the ASPL-TFE3 oncoprotein are not entirely elucidated. Some published evidence favors a dysregulating role in cell cycle and in cell signaling pathways. In cell cycle deregulation, attention has been drawn to senescence promotion through p21 up-regulation, bringing into play a suggested mechanism of tumor progression by senescence-associated secretory phenotype (SASP) via proinflammatory cytokines secretion [65–68].

In cell signaling kinase pathways, analyses on gene expression profiling have produced notable results. MET has been identified as a direct transcriptional target of the ASPL-TFE3 fusion. The latter binds to and activates the promoter, induces MET tyrosine kinase autophosphorylation increasing MET protein expression in the presence of its ligand hepatocyte growth factor, (HGF) and upregulates downstream signaling, as well as promoting cell proliferation, growth and invasion. This would seem to qualify MET as a basically suitable candidate for target therapy in ASPS [69, 70].

Proposed alternative targets of TFE3 include the transcription factor HIF-1a (hypoxia-inducible factor) whose activation upregulates certain angiogenic proteins (and their receptors) such as platelet derived growth factor, vascular endothelial growth factor A and angiopoietin 1/2 [32, 35, 71–74]. These data raise the possibility of effective anti-angiogenic therapies.

Other findings describe mRNA profiles with upgraded expression of MITF target gene, ML-IAP (melanoma inhibitor of apoptosis) which favors cell survival in melanomas [71, 75]. This in itself is not totally surprising as both MITF and TFE3 are members of the basic helix-loop-helix leucine zipper transcription factors family, along with TFEB and TFEC and both bind as homo- or heterodimers to a common DNA motif [65, 76, 77], the E-box DNA consensus sequence CANNTG.

In CGH array, initial studies described recurrent gains of 1q, 8q, 16q and Xp11-pter [78] along with complex aberrations (translocations, deletions, trisomy 12, trisomy 8, loss of chromosome 17 after chemotherapy) [79]. Updated results with high resolution aCGH confirmed these observations, suggesting increased chromosomal instability in the metastatic setting with new gains and losses but showed no consistent abnormalities other than genomic loss at 17q25 and large segmental gain at Xp [35].

Immunogenicity in ASPS has been but little explored in molecular genetics. Recent literature mentions significant increased expression of host response factors to the sarcoma involving the innate activating receptors TLR2 and TLR9 [59].

6.4.7 Differential Diagnoses

A wide spectrum of neoplastic diseases, mostly soft tissue and epithelial lesions, basically similar to ASPS in their morphological and cytological features must be distinguished from this tumor. The most common histotypes in that category include clear cell sarcoma of soft tissue, metastatic melanoma, clear cell renal cell carcinoma, adrenocortical carcinoma, clear cell endocrine/neuro-endocrine tumor, hepatocellular carcinoma (as mentioned, the liver can be a primary site of ASPS), granular cell tumor, PEComa, paranganglioma, alveolar rhabdomyosarcoma, clear cell rhabdomyosarcoma or rhabdomyoma.

All of these tumors lack the described specific non-reciprocal translocation which is the genetic hallmark of ASPS. It should be kept in mind that certain aspects such as significant or extensive atypia, cytoplasmic striations or a biphasic appearance generally rule out ASPS in its classical strikingly uniform architectural make-up. These mimics usually present with characteristic immunophenotypical particularities as well as being clinically distinct from ASPS for the most part. Paraganglioma generally occurs in older age groups [50] and are almost never observed in limbs; unlike ASPS, cytoplasmic glycogen is absent in tumor cells. Paraganglioma express neuro-endocrine markers while the accompanying sustentacular cells expressed S-100 protein [57].

Primitive clear cell sarcoma of soft tissue and metastatic melanoma usually express the melanocytic marker human melanoma black (HMB45), Melan A,

melanoma-associated antigen recognized by T cells (Mart-1) and S100 protein, although in metastatic melanoma those antigens may be lost. But like in ASPS, Cathepsine K is positive in melanoma. Clear cell sarcoma of soft tissue may likewise express focally cathepsine K but has a reciprocal translocation t(12:22) with the gene EWS RNA-binding protein 1 (EWSR1) fusing with activating transcription factor 1 (ATF1) in most cases [57].

Cells in granular cell tumor, like in ASPS, may contain PAS-resistant granules in an eosinophilic cytoplasm, and stain with TFE3 and cathepsin K antibodies but differ greatly from ASPS in that they lack cytoplasmic glycogen and intensely express PS100, SOX 10 and inhibin [57, 80].

Certain renal cell carcinomas, notably pediatric, share with ASPS the translocation (X;17) but in the reciprocal mode, the breakpoints being the same in both tumor types [81–83]. Test for reciprocity is possible by using the appropriate primers to the inactive fusion site [72]. Renal cell carcinomas, and not ASPS, stain with cytokeratin, epithelial membrane antigen (EMA) and paired box 8 (PAX8) and are negative for cathepsin K; hepatocellular carcinoma cells are positive for hepatocyte paraffin 1 (Hep-Par1), glypican-3, and polyclonal carcinoembryonic antigen (P-CEA) [57].

Neuro-endocrine or endocrine tumors are generally easily diagnosed, expressing neuromarkers or neuropeptides staining with antibodies against chromogranin, synaptophysin and CD56.

PEComas are often detected in the pelvis, gynecologic tract and retroperitoneum. Like ASPS a subset expresses TFE3 but unlike ASPS they all present by definition a double differentiation pattern, smooth muscle and melanocytic, staining with the corresponding specific antibodies (h-Caldesmon, HMB45, less often Melan A).

In adrenocortical carcinomas, Melan A or inhibin can be detected in principle by immunohistochemistry. Rhabdomyosarcomas are consistently positive for skeletal muscle differentiation markers (desmin, nuclear myogenin or MyoD1).

Some other lesions are much less likely to be confused with ASPS but can nevertheless, because of their epithelioid cytomorphology often displaying an abundant cytoplasm, be considered as differential diagnoses of the tumor in its less frequent solid or hyalinized appearances and lacking in alveolar configuration. These include epithelioid sarcoma, epithelioid angiosarcoma, epithelioid hemangioendothelioma, myoepithelioma, chordoma, meningioma or even malignant histiocytosis. But neither the immunohistochemical nor the molecular profiles of such lesions are consistent with ASPS.

6.5 Pediatric Specificities of Alveolar Soft Part Sarcoma

Alveolar Soft part sarcoma (ASPS) can occur in pediatric, adolescent or adult populations [48, 84]. In the large retrospective American SEER analysis, among 251 patients, the median age of occurrence of ASPS is 25 (range, 1–78), with 72% of patients younger than 30 years old. In pediatric, ASPS belong to the large group of non-rhabdomyosarcoma soft tissues sarcoma (NRSTS). Around 25% of all cases

occur in pediatric population (i.e. <18 years) and develop during adolescence (median age 10–16 years). This tumor represents 4.5% of all NRSTS occurring during childhood [85, 86]. The pediatric ASPS published series, all retrospective, confirmed that at diagnosis this tumor mainly occurs in limbs (63%), is confined in the organ of origin (T1: 73%) and is quite small (53% of tumor <5 cm) [87, 88]. Nodal involvement is rare (6% of all cases) and present only in patients with metastatic spreading. At diagnosis, distant metastases are frequent and represent up to 37% of all cases, which is the pediatric sarcoma with the most important rate of metastases at diagnosis (Fig. 6.5). In contrast to other adult-type soft tissue sarcomas arising in children, complete resection at diagnosis or after attempted of neoadjuvant chemotherapy is frequently possible (> 90%). Therefore, local tumor control is frequent but delayed metastases (pulmonary or brain metastases) are often encountered, sometimes years after initial diagnosis [84, 87].

Due to the rarity of this disease, no standardized treatment guidelines have yet been defined and are based on the adults' experience. Recently, various national European pediatric groups dealing with pediatric very rare tumors gathered themselves into a group called "EXPeRT" (*European Cooperative Study Group for Paediatric Rare Tumours*) and proposed dedicated guidelines for some very rare sarcomas, as ASPS (www.raretumors-children.eu) (Fig. 6.6). Primary surgery remains the mainstay of treatment: the achievement of microscopically complete

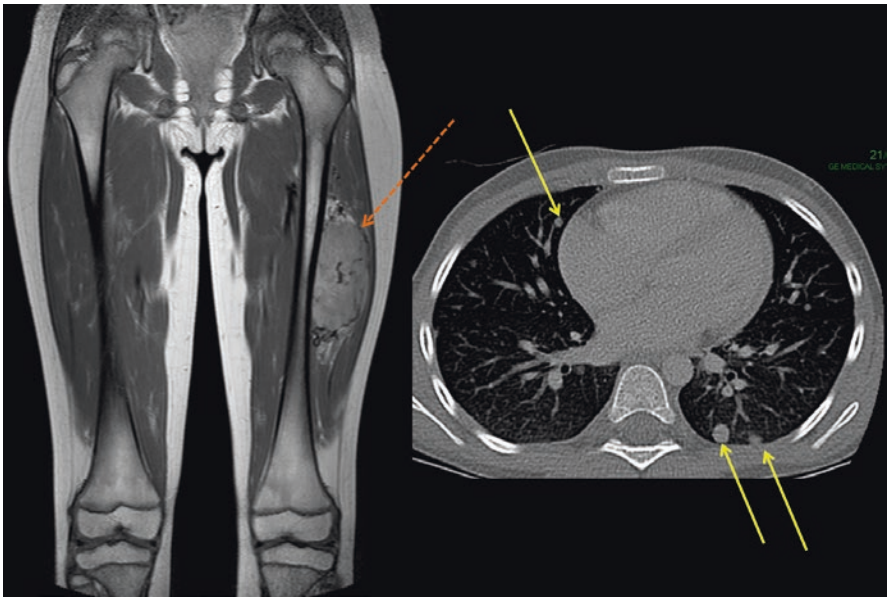

Fig. 6.5 Girl, 7 year old, with a stage IV thigh ASPS (dotted orange arrow) associated to multiple pulmonary metastases (full yellow arrows). No response to initial conventional chemotherapy and high dose regimen. Stable disease after 1 year of sunitinib. Local therapy with surgery (R0) and radiotherapy (50.4 Gy). Bilateral thoracotomy and thermal ablation of residual metastases. Absence of progression 3 years after the end of therapy

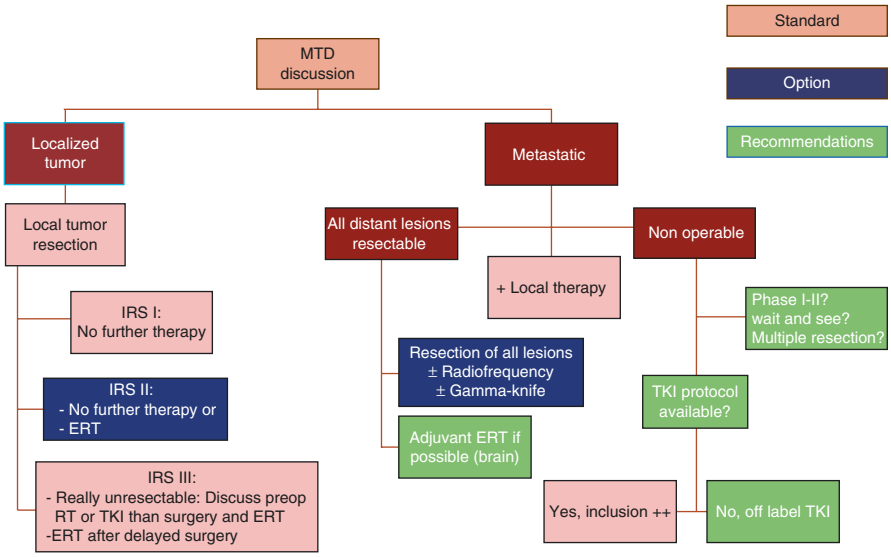

Fig. 6.6 Overall strategy proposed by the European pediatric very rare tumor group (*EXPeRT*) for alveolar soft part sarcoma

resection is critical in the case of localized ASPS. The role of local radiotherapy after surgery is not really defined in children. In children too, ASPS is chemoresistant to anthracyclin-alkylating based regimens and such drugs are not anymore advised in this sarcoma with an expected complete/partial remission rate less than 20% after conventional chemotherapy [48, 89]. Though the extreme rarity of ASPS in children hinders the feasibility of specific pediatric studies on this specific histiotype, recent data seemed to indicate that pediatric cases might deserve the same sensitivity, as adults, to new target agent as tyrosine kinase inhibitors [90, 91]. Overall, outcome seems more favorable in children with 5- and 10-year EFS of 68.2 ± 7% and 62.8 ± 7%; 5- and 10-year OS were 87.2 ± 5% and 78.0 ± 7%, respectively. As in adults, the main prognostic factor remains the presence of metastases at diagnosis [48, 86, 87].

6.6 Treatments

6.6.1 Surgery

In localized disease, complete resection is the optimal strategy but local relapse are frequent, ranging from 10 to 50% [2, 92]. R0 excision is critical but not always achievable. Surgery of metastasis has to be considered on brain metastasis due to the slow clinical course of the disease. Decision of metastasectomy is based on multidisciplinary discussion of each individual cases.

6.6.2 Medical Therapies

6.6.2.1 Chemotherapy

ASPS is a particularly chemoresistant entity. From a retrospective database, 47 adult patients and 13 children, treated by chemotherapy as a first-line treatment were collected and response rate to any chemotherapy regimen was low. Complete response (CR) were observed in 4% of patients, partial response in 3%, stable disease in 41% and progressive disease in 51%. In this study, about 30% of patients developed brain metastasis with a median interval from diagnosis of 48 months. Survival after evidence of brain metastasis was a year. Median survival of metastatic patients of any site was beyond 3 years [89].

Trabectidin, a marine-derived antineoplastic agent, was also tested in 2 small patient case series published in 2012. Both reported a good control rate but a low response rate with stable disease of 6 patients on 7 with a median progression-free survival (PFS) of 7 months, for the first study [93]. The second one tested trabectedin in translocation-related sarcomas and included 6 ASPS patients. All of them had stable disease (SD) [94].

6.6.2.2 Targeted Therapies

As chemoregimen lack efficacy in ASPS, targeted therapies were investigated with good results, offering a new spectrum of treatment options. Tyrosine kinase inhibitors (TKI) have an anti-angiogenic potential and target varied upregulated receptors including PDGFR, EGFR, VEGFR and RET.

Sunitinib

Sunitinib was the first investigated TKI in ASPS in 2009 [95, 96]. In first line setting, 15 patients received sunitinib between 2009 and 2015. Among them, 6 had PR (overall response rate of 40%), 8 had SD, and 1 had PD. The median PFS was 19 months. Median overall survival (OS) was 56 months with a 5-year OS rate of 49%. Five patients were treated with sunitinib longer than 2 years. The clinical benefit was observed in 93% of patients [97].

Pazopanib

In 2016, a Japanese study reported the efficacy of pazopanib in a STS patient population. Four on 12 patients with ASPS had a partial response (33%) [98]. Moreover, an international trial offered to test both trabectedin and pazopanib in a total of 44 ASPS patients [99]. As trabectedin managed mainly to stabilize patients (13/23 and

1 CR) with a PFS of 3.7 months, pazopanib reached a PFS of 13.6 months with a 27% ORR (7 PR, 1 CR, 17 SD).

Cediranib

Another potent VEGFR inhibitor, cediranib, was tested in metastatic ASPS through 2 open-label phase II trials. The first one conducted by Kummar et al. For the National Cancer Institute collected the response of 43 patients. Among them, 15 (35%) achieved a PR, 26 patients had SD [100]. The second phase II, led by Judson et al. from RoyalMarsden Hospital tested cediranib at a higher dosage of 45 mg (versus 30 mg in the previous study) on STS including GISTs. Four on the 6 ASPS patients had PR [101]. Both these enthusiastic results yielded to set up an international randomized phase II trial called CASPS (for Cediranib in ASPS). The results of this study were recently published in 2019. The proportion of patients with an objective response was 19% in the cediranib group versus 0% in the placebo group (one-sided p=0·072, cediranib vs placebo). No evidence of a significant difference in progression-free survival or overall survival between the treatment groups was observed, although, this analysis was probably confounded by the crossover to cediranib. Overall, the findings of this study support the concept that antiangiogenic therapy is active against advanced ASPS [102].

Other TKI

Dasatinib was tested in different kind of sarcomas. The highest 6 months-PFS observed was on ASPS subset of patients (62%), 2 year-PFS was 50%. Only one patient of the 10 included had an objective response [103]. Anlotinib has also been investigated in an early phase trial on refractory solid tumors and a response on lung metastasis was reported in a patient with ASPS [104]. Bevacizumab was also reported to have activity on an elderly patient [105].

Met Inhibitors

The chimeric ASPL-TFE3 fusion protein has recently shown impact on c-Met signaling pathway, as a possible transcriptional target. Tibantinib, a selective MET inhibitor was tested on MET related tumors including 27 patients with ASPS. Most patients has SD. No response was observed [70]. EORTC 90101 CREATE was one of the first ASPS specific prospective studies. The main objective of this phase II study was to assess the activity of crizotinib, a multi-targeted small molecule kinase inhibitor for MET, ALK, and ROS1 kinases in ASPS. The primary end point of the trial was not met, as objective response was observed in only one patient out of 40 with MET positive tumor (2.5% objective response rate; 95% confidence interval

[CI] 0% to 13.2%) and in patient out of 4 with MET negative tumors (25.0%; 95% CI 0.6% to 80.6%) [106].

6.6.2.3 Immunotherapy

There are several lines of evidence indicating that immune-checkpoint inhibitors are particularly active in ASPS. A phase 2 clinical trial of atezolizumab in metastatic ASPS enrolled 22 patients. Most participants had received prior treatments for metastatic disease, including TKIs. Eight out of the 19 patients (42%) who had been receiving atezolizumab had an objective response their tumors shrink (a partial response). Stable disease was observed in another nine patients. Several of these responses had lasted for more than a year at the time of data analysis. No serious side effects related to atezolizumab occurred during the trial [107]. Combination of immune-checkpoint inhibition with anti-angiogenic agent was assessed in a phase 2 trial including ASPS patients treated with axitinib plus pembrolizumab. This trial was the first to investigate combination therapy with an anti-VEGF receptor tyrosine-kinase inhibitor and an immune check point inhibitor in ASPS. Patients meaningful and durable objective responses. In the non-ASPS population, axitinib plus pembrolizumab had clinical benefit akin to other active sarcoma chemotherapy regimens including tyrosine-kinase inhibitors in the second-line or further lines of treatment. The 3-month progression-free survival was 72.7% (95% CI 37.1–90.3) [108].

6.6.3 Radiation Therapy

Radiation therapy is used in localized disease after surgery on tumors of the extremities for local control and in metastatic setting as palliative treatment, as applied to other sarcoma types [109].

6.7 Conclusion

ASPS is a rare sarcoma that arises in young patients and often metastasizes in lungs and brain. Despite its indolent natural history, long term prognosis is low. ASPS is known for its chemoresistance and TKI is the most widely used approach. Antiangiogenic agents and immune-checkpoint inhibitors appears as promising therapeutic strategies. Like for many sarcomas, only global collaboration lead to better understand this disease, may lead to its optimal management and offer best research perspectives. Moreover, the age frame of this disease strikes the need to collaborate between pediatric and adult oncologists.

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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].

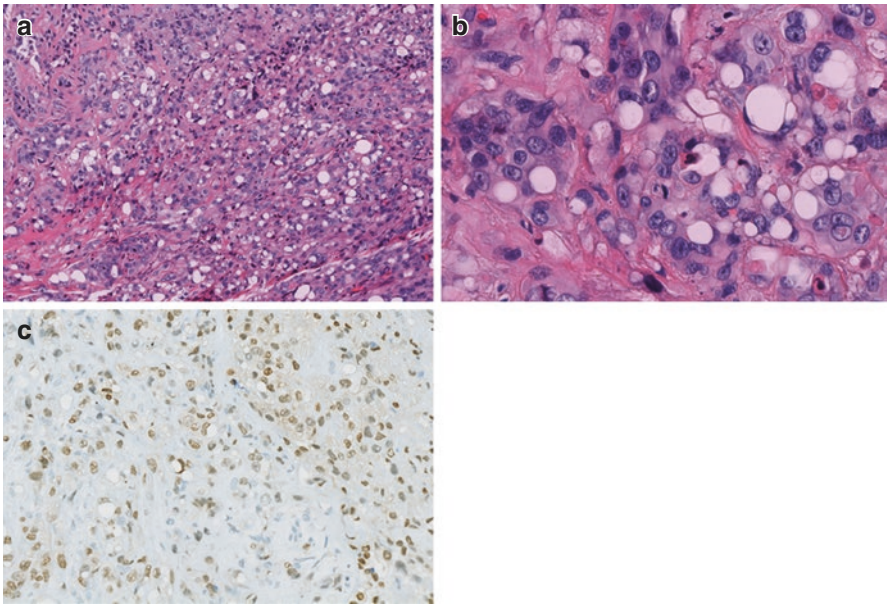

Fig. 7.1 Anatomopathological findings: (**a**) Epithelioid proliferation arranged in solid sheets with focal vacuolization (HES staining, ×150). (**b**) Tumor cells display vesicular nuclei and abundant eosinophilic cytoplasm containing intracytoplasmic vacuoles but no proper vascular lumen. This feature 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].

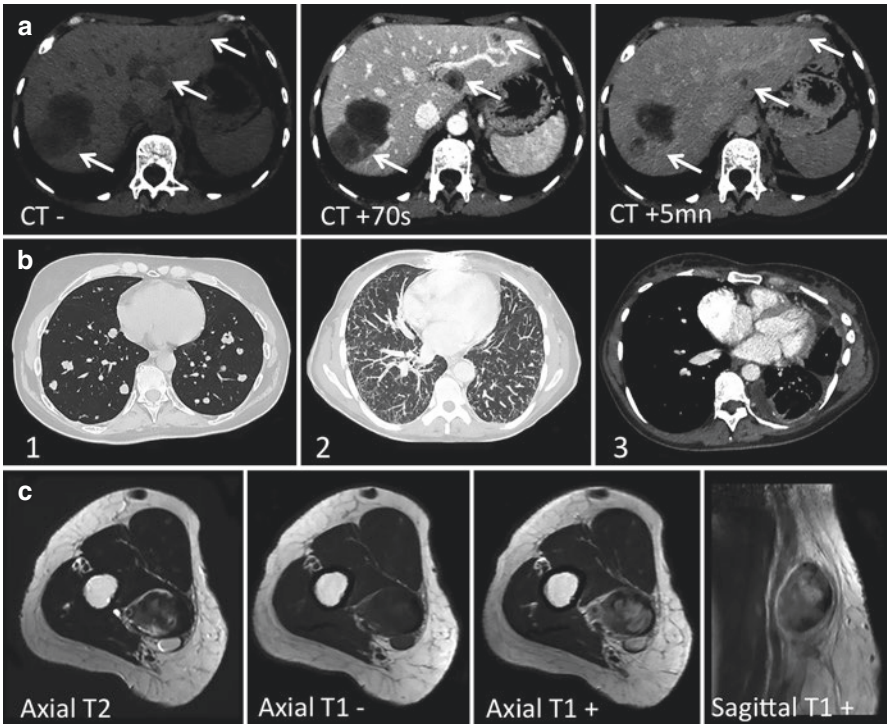

Fig. 7.2 Imaging features of the main locations of EHE. (**a**) Multifocal hepatic EHE including 2 subcapsular leisons (lateral, segment VIII and posterior, segment II-II). The largest one demonstrated low attenuation prior to iodine contrast agent injection (CT-), thick peripheral rim with focal reinforcements 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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Chapter 8
Low Grade Fibromyxoid Sarcoma/ Sclerosing Epithelioid Fibrosarcoma

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8.1 Introduction

Low-grade Fibromyxoid sarcoma (LGFS) and Sclerosing Epithelioid sarcoma (SEF) are two rare histologic subtypes of Soft Tissue Sarcoma (STS). The first description of LGFS was made in 1987 by Evans [1] in two patients having metastatic neoplasms with deceptively benign pathological appearance. Since this first report, LGFS have been widely described, and associated to the presence, in tumour cells, of a specific translocation involving *FUS* and *CREB3L2* genes.

SEF, another rare STS subtype, was first described in 1995 by Meis-Kindblom et al. [2], as an infiltrating and aggressive mesenchymal neoplasm, also associated to a specific translocation involving *EWS* and *CREB3L1* genes.

Many specialists consider LGFS and SEF as two related subtypes of STS. Indeed, overlapping forms have been widely described, either as hybrid pathological entities, or one of these pathological form harbouring the other's specific translocation.

That is the reason why we chose to consider them together in this chapter, possibly as two different parts of a common entity.

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8.2 Epidemiology

Due to its relatively recent genetic characterization and its rarity, LGFS incidence has only been evaluated in one study [3], based on a population-based Danish clinical database. The authors reported an estimated incidence of 0.18 cases per million. All data concerning LGFS is based on small retrospective of patients, the largest including 73 patients [4], and number of case reports.

SEF are rarer tumours, and no estimated incidence has been published so far. To this day, <150 cases of SEF have been published, either as small series (only four of them with more than ten patients [2, 5–7]) or case reports.

No specific risk factors have been identified for LGFS and SEF yet, both usually developing apart from any specific pathological context. However, both entities have been reported arising in previously irradiated fields [8–10].

8.3 Clinical Features (Table 8.1)

LGFS typically arise in young or middle-aged patients (median age at diagnosis surrounding 30 years in largest series [3, 4, 12, 14–17]. However, LGFS can occur at any age, and pediatric cases account from 8% to 37% in published series, with a few cases described in children under 5 years old [16, 18, 21–23]. Typically, LGFS present as a deep (82–93%, excluding one specific series of superficial LGFS [16]), painless mass. So far as we can judge from only two specific small retrospective studies [16, 18], subcutaneous LGFS seem to be more frequent in pediatric population. No gender preference can be strongly identified, either slight male or female predominance being alternatively reported by authors.

Lower limb is the most frequently involved site (36–65% cases), in particular at proximal sites. Other anatomical sites frequently involved are trunk or abdominal wall (18–45%) and the upper limb (0–22%). Head and neck location [24] are less frequent, accounting for 0–14% of LGFS. Rarely, LGFS can arise at other anatomical sites, including visceral organs as bowel [25], kidney [26], thyroid [27] or heart [28], and primitive brain location [29]. Median tumour size of LGFS at diagnosis ranges from 4.2 to 9.9 cm.

SEF also tends to arise in middle aged adults, yet older than LGFS (median age around 45 years), with no gender preference. Contrary to LGFS, SEF has never been described in young children (the youngest patients reported being 14 years-old [2, 5]. Anatomical repartition of SEF is similar to LGFS, most of tumours being deep seated, and developed at limbs, limbs girdle, or at the trunk. However, SEF arising at Head and Neck [30], Kidney [31–33], or primitive bone location [34–39] have been reported (Table 8.2).

Table 8.1 LGFS Patients' and tumours' characteristics in largest series (>10 patients)

	Folpe N = 73 [4]	Guillou N = 63 [11]	Evans N = 33 [12]	Hwang N = 29 [13]	Rose N = 23 [14]	Mertens N = 23 [15]	Billings[a] N = 19 [16]	Rekhi N = 18 [17]	Maretty-Nielsen N = 14 [3]	Sargar[b] N = 11 [18]	Oda N = 11 [19]	Goodlad N = 11 [20]
Median age: years	34	35	29	41	40,6	34	29	32,5	36	13	31	45
Pediatric cases: N (%)	14 (19)	5 (8)	3 (9)	NK	NK	2 (9)	7 (37)	NK	2 (14)	11 (100)	2 (18)	1 (9)
Gender: N (%)												
Male	40 (55)	24 (38)	19 (58)	14 (48)	10 (43)	12 (52)	12 (63)	9 (50)	5 (36)	NK	5 (45)	10 (91)
Female	33 (45)	39 (62)	14 (42)	15 (52)	13 (57)	11 (48)	7 (37)	9 (50)	9 (64)		6 (55)	1 (9)
Location: N(%)												
Upper limb	11 (15)	6 (10)	7 (21)	9 (31)	5 (22)	0	2 (11)	0	3 (21)	5 (45)	2 (18)	0
Lower limb	37 (51)	32 (51)	12 (36)	6 (21)	10 (43)	15 (65)	11 (58)	8 (44)	6 (43)	4 (36)	5 (45)	5 (45)
Trunk wall	20 (27)	15 (24)	6 (18)	8 (28)	7 (30)	6 (26)	5 (26)	6 (33)	3 (21)	0	3 (27)	5 (45)
Head and neck	4 (5)	1 (2)	2 (6)	3 (10)	0	1 (4)	0	3 (17)	2 (14)	1 (9)	1 (9)	0
Other	1 (1)	9 (14)	6 (18)	3 (10)	1 (4)	1 (4)	1 (5)	1 (6)	0	1 (9)	0	1 (10)
Median size (cm)	4.5	6	9.4	6.2	8.7	9	4.2	9.9	4.5	6	6.8	8.8
Situation: N (%)												
Deep	66 (90)	NK	30 (91)	27 (93)	NK	NK	0	NK	13 (93)	7 (64)	9 (82)	10 (91)
Superficial	7 (10)		3 (9)	2 (7)			19 (100)		1 (7)	4 (36)	2 (18)	1 (9)

NK not known
[a]Superficial tumours series
[b]Pediatric series

Table 8.2 SEF Patients' and tumours' characteristics in largest series (>10 patients)

	Wang N = 24 [7]	Meis-Kindblom N = 25 [2]	Antonescu N = 16 [5]	Prieto-Granada N = 10 [6]
Median age: years (range)	50	45	44	41
Pediatric cases: N (%)	1 (4)	1 (4)	1 (6)	NK
Gender: N (%)				
Male	10 (42)	14 (56)	6 (38)	1 (10)
Female	14 (48)	11 (44)	10 (62)	9 (90)
Location:				
Upper limb	1 (4)	12 (48)	4 (25)	3 (10)
Lower limb	1 (4)	2 (8)	3 (19)	2 (20)
Trunk wall	16 (67)	9 (36)	4 (25)	1 (10)
Head and neck	2 (8)	2 (8)	5 (31)	2 (20)
Other	4 (17)	0	0	2 (20)
Median size (cm)	NK	7	9	9.2
Situation: N (%)				
Deep	NK	25(100)	NK	10 (100)
Superficial		0		0

NK not known

8.3.1 Imaging Fidings

8.3.1.1 LGFS

Two series [13, 18], (including a pediatric series), have reviewed LGFS' imaging findings. Both show similar results, with typical tumoral CT features showing heterogeneous density, with most areas hypodense to muscle, and peripheral or internal enhancement on contrast-enhanced CT. One of the authors reported the presence of calcifications in rare cases [13].

Typical features in MRI show LGFS as circumferentially well-defined tumours [18], with heterogeneous signal. On T1-weighted images, most of tumours show predominant hypointense signal (only rare cases having predominant isointense signal with some hypointense areas). On T2-weighted or STIR images, LGFS are predominantly hyper or isointense to muscle, with frequent peritumoral oedema. On contrast-enhanced RMI, enhancement is present in all tumours, but ay very disparate levels between cases. Global massive enhancement is present in one third of the tumours, whereas another third show partial and the last third show low (involving less than one third of tumour) enhancement (Fig. 8.1). In a subset of cases, enhancement appears to be peripheral, with a giriform nodular pattern.

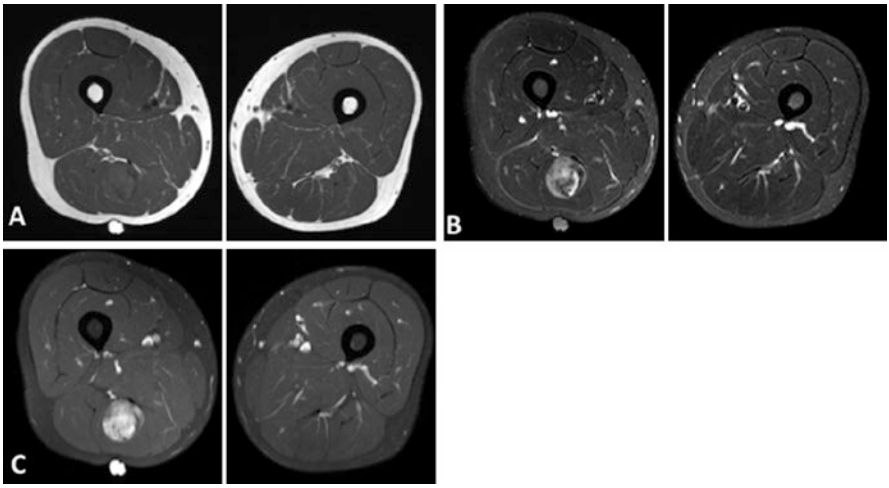

Fig. 8.1 MRI typical features of a 34 years old patient with LGFS of the right thigh. Tumour presents as a well circumscribe mass, with iso/hypointense T1 signal (**a**), high T2 signal (**b**), and massive enhancement after gadolinium injection (**c**). Personal data

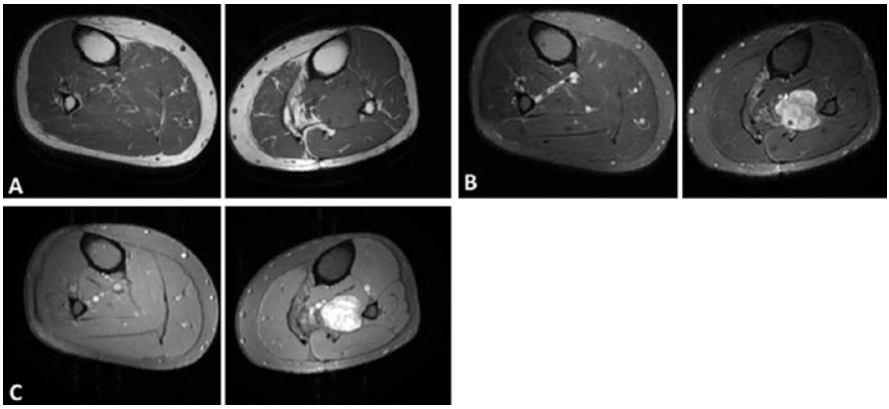

Fig. 8.2 MRI typical features of a 64 years old patient with SEF of the left leg. Tumour presents as a well circumscribe mass, with iso/hypointense T1 signal (**a**), high STIR signal (**b**), and massive enhancement after gadolinium injection (**c**). Personal data

8.3.1.2 SEF

No study ever compiled radiologic features of SEF yet. However, rare data coming from case reports suggest than SEF imaging features (CT and MRI) seem to be very similar to LGFS (Fig. 8.2).

8.3.1.3 Nuclear Medicine Imaging

Both LGFS [3, 40–42] and SEF findings in fluorodeoxyglucose positron emission tomography (FDG-PET) [43–46] have been the subject of case reports. All authors showed mild abnormal FDG accumulation in both subtypes.

8.3.2 Pathological Findings

8.3.2.1 Macroscopy

LGFMS usually appears as a well-circumscribed mass with a white fibrous cut surface, often with glistening mucoid areas [12, 47, 48].

SEF usually present as a grossly circumscribed, lobulated or multinodular mass with a firm, whitish cut surface. Myxoid, cystic, and calcified areas may be seen as well. Necrosis is uncommon [5, 11, 47, 48].

8.3.2.2 Histopathology

Low-grade fibromyxoid sarcoma shows characteristic pattern with both fibrous and myxoid stroma (Fig. 8.3). The hyalinised hypocellular areas are juxtaposed to more cellular myxoid nodules associated with curvilinear to branching prominent vasculature and arteriole-sized vessels with perivascular sclerosis. The tumor shows bland and scattered spindle to stellate cells, with small, angulated nuclei with inconspicuous nucleoli and scant, wispy cytoplasm. They are arranged in a whorled growth pattern usually showing an abrupt or gradual transition from myxoid to densely collagenized areas [12, 47, 48]. Mitotic figures are absent or sparse, although a mitotic index of >5/50 high power fields and tumor cell necrosis can be seen in <10% of cases. A curvilinear capillary network, similar to that seen in low-grade myxofibrosarcoma, has been noted frequently in the myxoid areas. Hyalinising spindle cell tumor with giant rosettes (HSCTGR) is a morphological variant of LGFMS and is also characterized by a proliferation of bland-appearing spindle cells in fibromyxoid areas with presence of poorly formed collagen rosettes, consisting of hyalinised, eosinophilic acellular islands surrounded by oval, epithelioid and spindle cells in a palisading pattern [4, 49]. LGFMS may display some unusual features as increased cellularity, marked nuclear atypia and pleomorphism, epithelioid morphology mimicking sclerosing epithelioid fibrosarcoma.(SEF). Rarely tumor shows cyst formation, calcification, foci of bone formation, prominent hemangiopericytoma-like vasculature and tumor necrosis [17, 47, 48].

The earliest observation of LGFMS cases with areas resembling what is now known as SEF was provided by Evans in 1993 [50], which was interpreted as

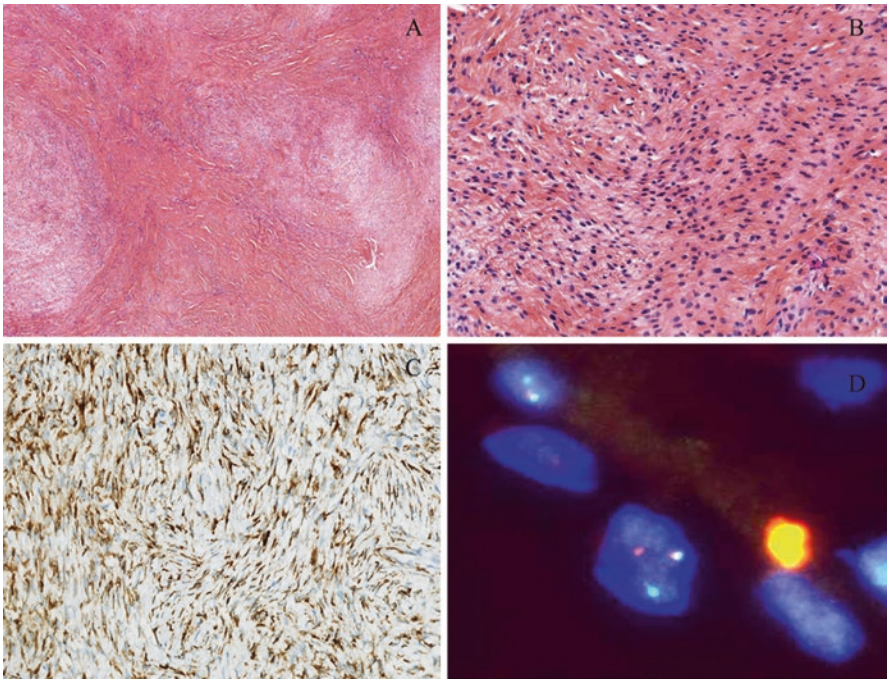

Fig. 8.3 Low-grade fibromyxoid sarcoma. (**a**) Abrupt transition from hyalinized to myxoid nodules; (**b**) Bland spindle cells embedded in a collagenous background; (**c**) Diffuse cytoplasmic immunoexpression of MUC4; (**d**) Dual-colour FISH with a probe-set flanking *FUS* gene demonstrates the presence of a rearrangement of this locus in tumour interphase nuclei (split red and green signals). Personal data

evidence of "dedifferentiation". Hybrid SEF/low-grade fibromyxoid sarcoma (SEF containing areas indistinguishable from LGFMS) also occur [38] and hybrid SEF/LGFMS can show either predominantly SEF or LGFMS morphology, and may include giant collagenous rosettes [6].

SEF is a sclerosing or densely hyalinized tumor with nests and cords of small to moderate-size epithelioid cells with angulated, round, bland or ovoid nuclei and scant clear to eosinophilic cytoplasm (Fig. 8.4). These cells are embedded in sclerotic to fibrohyaline, eosinophilic extracellular matrix [2, 5], imparting an appearance resembling carcinoma, lymphoma, chondrosarcoma or even paraganglioma. Fibroma-like and hypocellular myxoid areas resembling low grade fibromyxoid sarcoma are seen as well as degenerative myxoid cysts and foci of metaplastic bone and calcification [2, 47, 48]. Blood vessels of the tumors are usually thin walled and ectatic with a haemangiopericytoma-like disposal. Mitotic activity can be relatively low at 4–5 mitotic figures per 10 high power fields, and necrosis is generally present in fewer than half of cases [6].

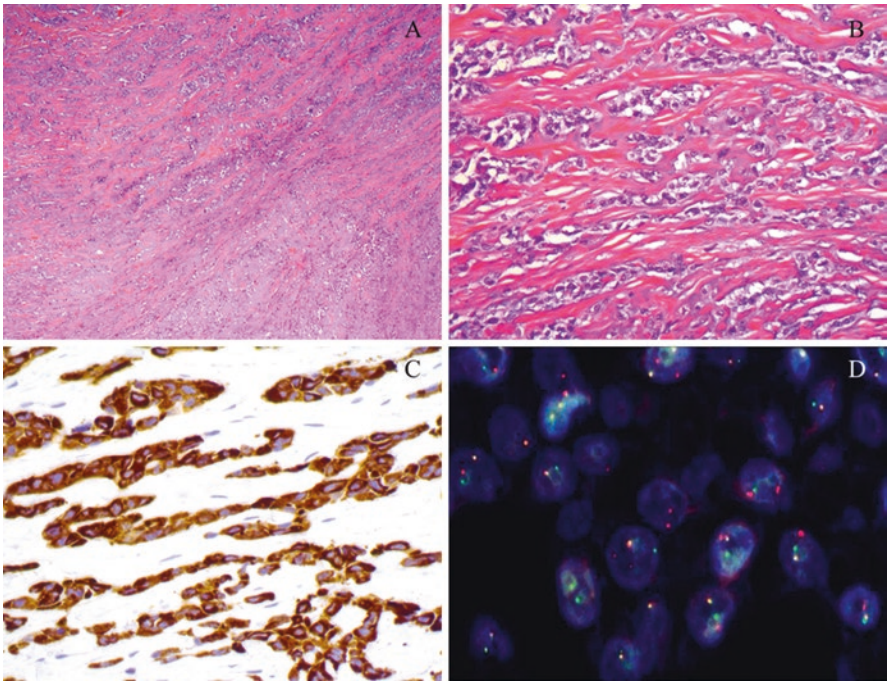

Fig. 8.4 Sclerosing epithelioid fibrosarcoma. (**a**) Prominent hyalinized collagen matrix associated with small epithelioid bland cells arranged in cords; (**b**) Typical nested, corded and pseudoalveolar growth patterns and prominent sclerotic collagen matrix; (**c**) Diffuse cytoplasmic immunoexpression of MUC4; (**d**) Dual-colour FISH with a probe-set flanking *EWSR1* gene demonstrates the presence of a rearrangement of this locus in tumour interphase nuclei (split red and green signals). Personal data

8.3.2.3 Immunohistochemistry

MUC4, a high molecular weight transmembrane glycoprotein, shows strong and diffuse granular cytoplasmic immunoreactivity up to 100% of LGFMS [51] (Fig. 8.3). MUC4 is normally expressed on many epithelial surfaces [52] and is overexpressed in a wide range of adenocarcinomas. Although MUC4 immunohistochemistry is highly sensitive for LGFMS, MUC4 expression is seen in other spindle cell or epithelioid neoplasms, including biphasic synovial sarcomas, predominantly in the glandular areas, ossifying fibromyxoid tumors, epithelioid gastrointestinal stromal tumors and myoepithelial carcinomas [53]. Except MUC4 expression, the immunohistochemical findings in LGFMS are relatively nonspecific. Several LGFMS are focally positive for EMA. Focal positivity for smooth-muscle actin (SMA), desmin, CD34, and cytokeratin is rarely seen. LGFMS are negative for S100 protein, H-caldesmon and MDM2.

The strong and diffuse immunohistochemical expression of MUC4, which is a consistent finding in LGFMS, is also seen in approximately 78% of SEF, including 100% of hybrid LGFMS-SEFs [53] (Fig. 8.4), lending further weight to the possibility of a close relationship between these tumors. Focally and weakly reactive for EMA and S100-protein may be seen. Other stains, including those for

keratins AE1/AE3, HMB45, CD68, GFAP, smooth-muscle actin, desmin, and CD34 are negative [47, 48, 53].

8.3.2.4 Molecular Characteristics

Most of the LGFMS (>90%) show fusion transcript resulting in fusion of the *FUS* and *CREB3L2* (also known as BBF2H7) genes t(7;16)(q33;p11) with breakpoints always localized in exons 6 or 7 of *FUS* and exon 5 of *CREB3L2* [11, 54, 55] (Fig. 8.3). A rare variant results in a *FUS-CREB3L1* fusion t(11;16)(p11;p11) [56] and, recently, Lau et al. reported an *EWSR1-CREB3L1* fusion in two cases [57].

The majority of pure SEF tumors harbour *EWSR1* rearrangements, with *EWSR1-CREB3L1* (Fig. 8.4) and to a much lesser extent, the *EWSR1-CREB3L2* fusions more common than those involving *FUS* gene [6, 7, 58–60]. One case of *EWSR1-CREB3L3* genes fusion in a mesenteric SEF was recently described [61].

In contrast, similar to LGFMS, in hybrid tumors with histologic features of both LGFMS and SEF, Both types of rearrangements can be be found, a vast majority of hybrid tumours harbouring *FUS*/*CREB3L2* rearrangement [6] although *EWSR1* rearrangements can be present in smaller numbers [53, 60].

8.3.2.5 Differential Diagnosis

The morphologic diagnosis of LGFMS may be challenging, owing to its bland cytomorphology and low cellularity. The differential diagnosis of LGFMS includes several benign tumors (nodular fasciitis, perineurioma, neurofibroma, myxoma, desmoplastic fibroblastomas), tumors of intermediate malignancy (desmoid fibromatosis, ossifying fibromyxoid tumor, dermatofibrosarcoma protuberans) and malignant tumors (low-grade myxofibrosarcoma, dedifferentiated liposarcoma). It is important to distinguish it from benign or low-grade fibromyxoid lesions, because of the significant potential for recurrence and late metastatic spread.

SEF can be difficult to distinguish from tumors with epithelioid/round cell morphology, such as carcinomas (especially breast lobular carcinoma), melanomas, small round cell tumors, and myoepithelial tumors. Immunohistochemistry is useful in this instance primarily to exclude these histologic mimics. The prominent sclerotic extracellular collagenous matrix of SEF can be mistaken for tumoral osteoid leading to diagnostic confusion with osteosarcoma.

8.4 Treatment of Localized Disease

Amongst largest retrospective studies, only seven include at least a partial overview of the treatment of patients with LGFS (Table 8.3). In nearly all case, patients received an exclusive surgical treatment. By analogy to other STS subtypes, some patients underwent multiple surgeries, in order to get tumoral free margins. Less

Table 8.3 Treatment and follow-up of patients with localized LGFS in largest series (>10 patients)

	Folpe N = 73 [4]	Guillou N = 63 [11]	Evans N = 33 [12]	Rose N = 23 [14]	Mertens N = 23 [15]	Billings N = 19 [16]	Rehki N = 18 [17]	Maretty-Nielsen N = 14 [3]	Oda N = 11 [19]	Goodlad N = 11 [20]
Case with treatment information	54	0	33	18	0	NK	18	14	11	0
Surgery	51 (94)	NK	33 (100)	18 (100)	NK	NK	17 (94)	12 (100)	11 (100)	11 (100)
Adjuvant RTE	4 (7)	NK	5 (15)	0	NK	NK	NK	1 (8)	0	1 (9)
Adjuvant chemo	2 (4)	NK	1(3)	0	NK	NK	NK	0	0	0
Cases with follow up	54	28	33	18	22	16	12	14	8	11
Local relapse: N (%)	5 (9)	6 (21)	21 (64)	0	5 (23)	2 (13)	3 (25)	4 (28)	4 (50)	6 (55)
Median time to LR	NK	276 months	3.5 years	NA	(19–155 months)	5 and 16 months	NK	4.1 years	24 months	4 years
Metastatic relapse: N (%)	3 (6)	6 (21)	15 (45)	0	6 (27)	0	1 (8)	3 (21)	0	1 (9)
Median time to MR	NK	132 months	5 years	NA	5 years	NA	NK	NK	NA	9 years
Death of disease % (median time)	2% (NK)	0	42% (15 years)	0	0	0	0	7% (12 years)	9% (54 months)	NK

RTE radiotherapy, *LR* local relapse, *MR* metastatic relapse, *NK* not known, *NA* not applicable

than 10% of patients (out of 158) received adjuvant radiotherapy, and only three patients adjuvant chemotherapy.

Treatment of SEF is also extrapolated from other STS data. In retrospective series and cases reports, surgery remains the treatment of choice for most patients [62], eventually followed by radiotherapy for a subset of patients. Adjuvant chemotherapy was rarely used too.

8.5 Prognosis

LGFS were initially described as aggressive tumours, with high recurrence rates. In the most recent update of the historical series of patients with LGFS [12], local and distant recurrences occurred respectively in 64% and 45% of patients. In other series, in particular in largest series [4, 11], LGFS behavior seems to be slightly different and more indolent, with local and metastatic recurrence rates ranging from 0% to 55%, and from 0% to 27% respectively (Table 8.3). As frequently described in low grade sarcomas, relapses can occur several years after diagnosis, with median time to relapse ranging from 2 to more than 20 years. The same discrepancy exists concerning disease mortality. In Evan's initial series, 42% of patients died because of their disease, strikingly higher than in other studies (0–9%).

The small number of patients included in retrospective series does not allow us to evaluate prognostic factors for LGFS. However, as in other STS, surgical margins are thought to be determinant in local control [11, 12]. In contrast, neither tumour size, nor the presence of pathological "high-grade" focal areas seem to carry any prognostic value. Compared with deep tumours, superficial LGFS seem to have better outcome [16].

Retrospective data concerning SEF suggest that is carries worse prognosis than LGFS (Table 8.4). Indeed, in largest series, local and metastatic rates account for

Table 8.4 Treatment and follow-up of patients with localized SEF in largest series (>10 patients)

	Wang N = 25 [7]	Meis-Kindblom N = 25 [2]	Antonescu N = 16 [5]	Prieto-Granada N = 10 [6]
Case with treatment information	16	0	16	0
Surgery	NK	NK	16	NK
Adjuvant RTE	NK	NK	9	NK
Adjuvant chemo	NK	NK	4	NK
Cases with follow up	16	16	14	7
Local relapse: N (%)	NK	8 (50)	7 (50)	3 (43)
Median time to LR	NK	4.8 years	23 months	24 months
Metastatic relapse: N (%)	12 (75)	4 (25)	12 (85)	5 (71)
Median time to MR	NK	7.7 years	22 months	15 months
Death of disease: % (median time)	31% (22 months)	25% (4.8 years)	50% (26 months)	33% (118 months)

RTE radiotherapy, *LR* local relapse, *MR* metastatic relapse, *NK* not known, *NA* not applicable

43% to 56% and 44% to 85% of patients, respectively. As a confirmation of SEF status of "high grade STS", they also relapse earlier than LGFS, most of them within the 2 years following treatment.

8.6 Treatment of Local or Metastatic Relapses

Lung is the most frequently reported site of metastatic relapse of patients with LGFS. Less frequently, metastasis involve pleura, subcutaneous tissues, bone, heart. When possible, both local and metastatic relapses treatments relied on surgery [11]. No evaluation of chemotherapy (in particular anthracycline) efficiency has been described in this low-grade sarcoma, with low mitotic count. However, one patient [3] received many chemotherapy protocols, and had as best result a short-term disease control with trabectedin, already known to offer benefit in the treatment of translocated-related sarcomas.

Surprisingly considering the rarity of SEF, but in accordance with the higher aggressiveness compared to LGFS, more data are published concerning chemotherapy effect in SEF. However, only three cases of patients treated with different protocols have been published, with various outcomes. Tomimaru related the case of one patient treated with a combination of doxorubicin and ifosfamide (as analogy with other STS), and showed short disease control without tumoral shrinkage [44]. Another 16-years patient [36] was treated with a combination of cisplatin/doxorubicin and high dose methothrexate, with no evidence of tumour response. The third case report showed an objective and unprecedented response of a patient with metastatic SEF treated with irinotecan [63].

8.7 Conclusion

LGFS and SEF are two rare subtypes of STS, supposed to be related to each other by their similar genetic background. However, their clinical evolution differs, LGFS having a behavior resembling other low grade sarcomas (with local relapse as main risk and low specific mortality), whereas SEF act like higher grade sarcomas (with early metastatic evolution and high disease specific mortality). For both diseases, prognostic factors, in particular the prognosis value of the different specific translocation, have to be investigated. Moreover, their optimal treatment remains unclear, and has yet to be extrapolated of other STS. In order to improve our knowledge of these rare STS, we need prospective research programs. This is currently under consideration within the French Sarcoma Group (GSF/GETO) centers, in the context of a Rare Sarcomas global project.

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Chapter 9
New Born and Infant Soft Tissue Sarcomas

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9.1 Introduction

Sarcomas occurring in children under 1 year old are rare situation [1]. In an international multicenter study, predominantly European, infant sarcomas (i.e., occurring before 1 year of age) account for 8% of all pediatric soft tissue sarcomas. These tumors can be revealed during the perinatal period, sometimes prenatally during the fetal echography of the last trimester or more frequently during first months of life. It appears clinically most often as a voluminous mass developing in the soft tissue, rapidly progressive (Fig. 9.1). Clinically, the mass is firm and painless. This latter may

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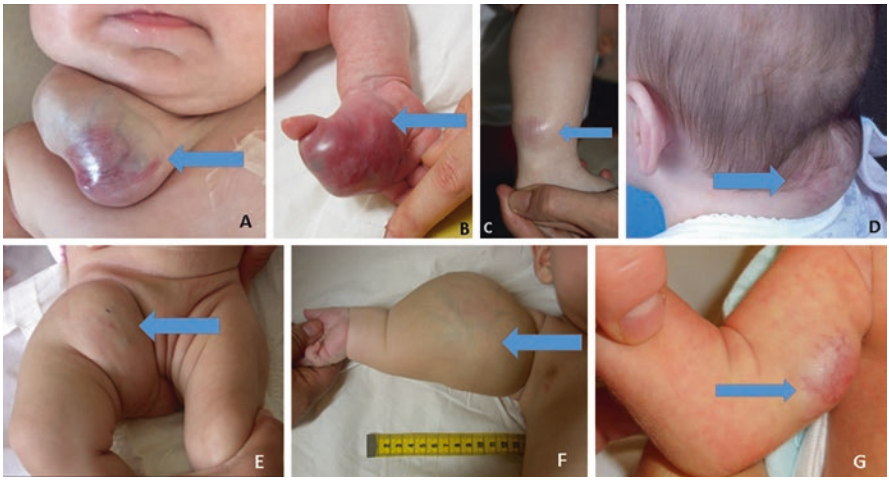

Fig. 9.1 Clinical aspect of some infants soft tissue sarcomas: (**a**) 4 months, cervical rhabdoid tumor, (**b**) 2 months, thumb rhabdoid tumor, (**c**) 3 months, leg infantile fibrosarcoma, (**d**) 2 months, cervical Ewing sarcoma, (**e**) 2 months, inguinal infantile fibrosarcoma, (**f**) 2 months, upper limb congenital fibrosarcoma, (**g**) 2 months, arm myofibroma

sometime be associated to severe life threatening situations as cervical compression or hemostatic abnormalities (alveolar rhabdomyosarcoma, diffuse rhabdoid tumor) even if thrombocytopenia and consumptive coagulopathyare more frequently seen in neonatal benign hemangioendothelioma with Kasabach-Merritt syndrome [2]. At this age, in front of a mass occurring in soft part tissue diagnostics range is wide. Malignant lesions are much less common than benign lesions. The clinical aspect is not very specific and the imaging exams have many pitfalls making the exact diagnosis often difficult. Infectious disease or developmental abnormalities can mimic some tumors. The diagnostic orientation is mainly based on the interpretation of radiological examinations (X-ray and soft tissue ultrasound) in first line, but MRI is often necessary [3]. Imaging analysis allows identifying some typical benign lesions (such as infantile hemangiomas, fibromatosis coli, benign lipomatous tumors or pilomatricomas) and consequently to avoid unnecessary biopsy. Conversely, when clinical and radiological analyses cannot identify a typical benign mass (i.e. demonstrating a "non-specific" or a "suspicious" mass), an image-guided core needle biopsy should always be performed.

Initial surgical approach should be avoid, especially in infants, because: many lesions could be left in place (hemangiomas, post-traumatic lesions, fibromatosis tumors); some lesions require non-surgical treatment first with chemotherapy (sarcomas), medical treatments (some hemangiomas, fibromatosis tumors), or percutaneous treatment (venous malformations), and surgical approach should be different according to histology, as sarcomas who need wide delayed resection to get free margins at the opposite of benign lesions that require initial conservative surgery.

Proportion of benign tumors, malignant tumors and pseudo-tumors at this age is not well defined. In the Institut Curie imaging department experience in Paris, 21% of all soft tissue, necessary selected, masses sent to the Pediatric Oncology Department of the Institut Curie before the age of 1 year were malignant (Fig. 9.2)

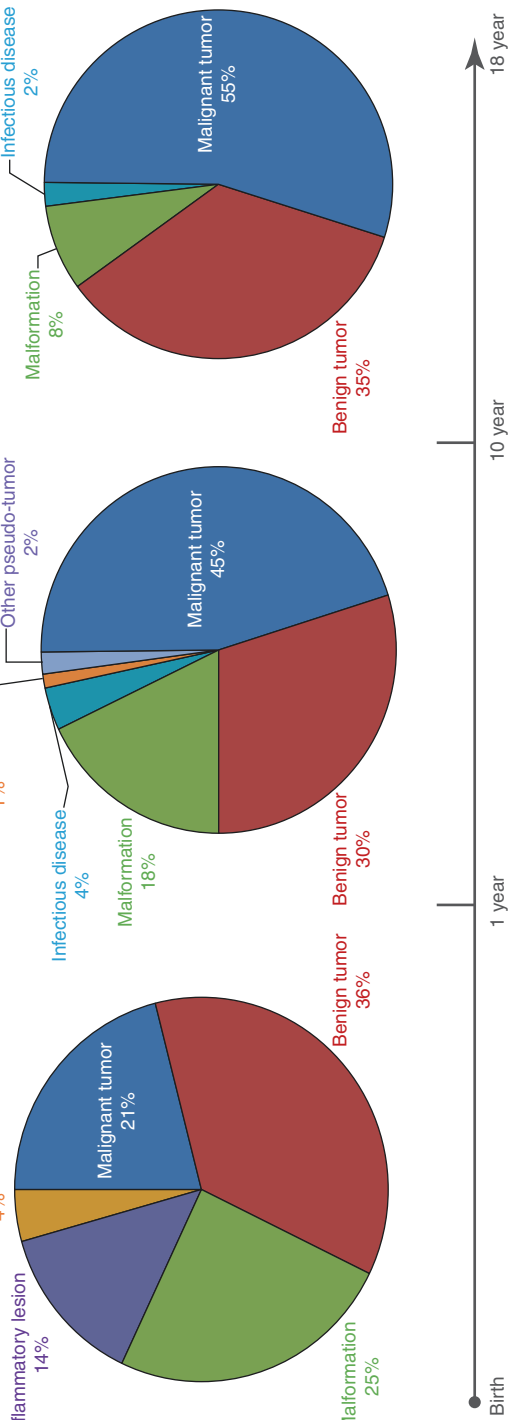

Fig. 9.2 Distribution of soft part tissue lesions diagnosis according to age of onset, the Institut Curie experience (adapted to Papillard-Marechal S et al. with authors' permission, Arch Pediatr. 2015 Jan;22(1):14–23.)

[4]. At this age, main sarcomas were infantile fibrosarcomas (IFS; around 25% of all cases) and rhabdoid tumors (35%) [1, 5]. Rhabdomyosarcoma (15%) and undifferentiated sarcomas (25%) can also occur. Locally infantile aggressive fibromatosis are often difficult to treat and are considered as intermediate malignancies. To better characterize these rare tumors, different national European groups dealing with pediatric very rare tumors, grouped themselves into a group called "EXPeRT" (*European Cooperative Study Group for Paediatric Rare Tumours*) and propose dedicated guidelines for some very rare sarcomas, as infantile fibrosarcoma (www.raretumors-children.eu).

Overall strategy should take into account the age and the medical condition of the young patient. Surgery is a cornerstone of therapy, chemotherapy should be adapted to the immature organs and radiotherapy should be avoid as possible due to their potential late consequences in infants, mainly organs growing retardation, organ dysfunction, and secondary malignancies. In addition, in some very large extensive aggressive diseases, as neonatal metastatic rhabdoid tumors, ethical considerations should be taken into account and medical decisions must strongly consider parents' opinion after having clearly informed them of the seriousness of the oncological situation and the consequences of therapies when delivered at this age.

9.2 Specificities of STS Surgery in Infant

Soft tissue sarcoma (STS) surgery in infant requires a multidisciplinary approach with clinicians, surgeons, radiologists and pathologists to define the appropriate treatment. Soft tissue tumors are mostly benign in infants as vascular tumors. As differentiating benign tumors and sarcomas may be difficult on radiologic exams at this age, in doubt, the surgical treatment begins with the biopsy for which the technique and the surgical approach must be discussed according to the imagery, de location and the future surgical approach for total removal. An initial cytology can be carried out by fine needle aspiration to oriented diagnosis, which has the advantage of being minimally invasive and performed only under local anesthesia. This technique is very interesting in infants considering the risks of general anesthesia at that age. In case of failure or remaining doubtful diagnosis, a percutaneous micro-biopsy or a surgical biopsy can be performed with systematic freezing of a part of the sample for cytogenetic and molecular studies. These studies will allow in addition identifying the presence of a fusion transcript and thus having a precise diagnosis of the tumor [6].

Surgical strategy depends on the histological type [2]. The treatment is always first discussed in a multidisciplinary manner. Treatment protocol may include first systemic chemotherapy than local therapy with surgery and rarely radiotherapy. For some diseases, surgery could be the unique therapy. The STS surgery in infant is nevertheless challenging because of the size of the child and the proximity with neuro-vascular bundles possibly originating important functional sequelae. The decision to use radiotherapy is often taken on a case-by-case basis but there is a

tendency to avoid radiotherapy for completely resected tumors because of its long-term toxicity at this age. For IFS, primary surgery after initial biopsy currently remains the mainstay of treatment but the surgical approach has evolved over the years, from being the only treatment to being an important part of a multidisciplinary strategy [5]. In such tumor, mutilating surgery should only be proposed after failure of all other treatments. Initial non-mutilating complete resection is feasible in less than one-quarter of infants and, therefore, surgery should often be considered as the final step of a multimodal approach starting with chemotherapy. Some studies previously reported the very good overall survival of children with IFS, and emphasized the challenge of tumor resectability without anatomical or functional damage [7]. In some cases, chemotherapy as sole treatment can also achieve complete remission of the tumor without surgery. In cases where tumor shrinkage is obtained with chemotherapy but surgery remains mutilating, simple biopsies may be proposed in the remaining residue before proposing a more aggressive local treatment or more frequently a second line therapy. In such case, the role of new targeted drugs as *NTRK* inhibitors (larotrectinib) is very promissing [8].

The strategy is very different for neonatal RMS and malignant rhabdoid tumor due to highly aggressive neoplasm. Overall, children <1 year of age often have unfavorable features and advanced disease for RMS. Rhabdoid tumors are very rare, aggressive and frequently lethal. The treatment is based on chemotherapy and local therapies (surgery and/or sometime radiotherapy). Intensity and timing of treatment needs to be risk-stratified to provide the best chance for cure and to minimize late treatment toxicity in infant. Radiotherapy is an essential resource in the treatment of patients with RMS but the awareness of possible sequelae raises special challenges in the very young child [1]. Considering the poor prognosis of these tumors, the total oncologic resection is mandatory to insure the best chances of survival and avoid if possible radiotherapy. Conservative surgery is not always possible because of the young age and the close neuro-vascular bundles. Reconstructive surgery by bypass or nerve grafts are difficult at that age and not always possible. Radical surgery with limb amputation should be considered in these tumors when conservative surgery is not possible.

9.3 Role and Management of Chemotherapy Before the Age of 1 Year

Chemotherapeutic agents used to treat pediatric cancer, and especially soft tissue sarcomas, are generally close to the adult's chemotherapeutic molecules. It includes conventional cytotoxic drugs and, to a lesser extent, molecularly targeted agents. Both malignant and normal cells could be the target of the cytotoxic agents. This effect on the normal and developing cells in infants is the cause of main adverse events. In fact, the management of chemotherapy in children younger than 1 year of age has to be considered in a developing organism with maturing organ function and physiologic differences (i.e., body composition or affinity to plasma protein) but

also in a pharmacogenetic manner [9, 10]. Except targeted therapy, cytotoxic drugs are quite all administered intravenously (IV) for the treatment of soft tissue sarcoma in childhood, this explain why the absorption is not specifically a problem in infants. However, in case of an oral treatment, different physiologic aspects may interfere with absorption. Gastrointestinal motility is low at birth and increase to adult values by 6–8 months old increasing or decreasing the absorption. Gastric pH is neutral during the first months and reach the adult values at 2 years old, which modify the bioavailability of drugs [11]. Therefore, galenic of treatment is not often specifically designed for infants and extemporaneous formulations from IV vials are mainly used. After absorption or IV infusion, drugs diffuse out of vessels and the expansion to tissues in so-called volume of distribution (Vd). Vd is partly influenced by body composition. The proportion of extracellular fluid volume represent 50% of body weight in preterm newborn, 35% in infants from 4 to 6 months old and 20% in adolescent and adult. Thus, a larger Vd leads to a lower concentration peak. Fat component and blood protein level interfere also in Vd. In addition, during infancy the immaturity of blood-brain barrier enable a better diffusion of drugs in the central nervous system.

Moreover, kidney and liver manage cytotoxic drug excretion. Drug metabolism is primarily handled by the liver. Enzymes involved in phase I and II reactions are still in maturation in newborn and infant. At birth, CYP450 enzymes (phase I) have low activity, which increase during childhood, reaching adult level during puberty. Reactions of conjugation (phase II) like glucuronidation are low at birth then reach adult level by 6–12 months [12]. Maturing functions during infancy are the causes of unpredictable changes in hepatic drug metabolism. The glomerular filtration rate (GFR) is low at birth and increases to adult value at 6–12 months which explains why the plasma half-life of certain cytotoxic drugs can be prolonged. In addition, tubular function and biliary excretion are also low at birth and reach adult values respectively at 1–2 years and 6 months. Furthermore, immaturity of drug transport function strongly modifies drug metabolism in comparison to older children.

Currently, dosing of anticancer delivered drugs in newborn and infant is based on body weight instead of body surface area for older children. However, due to the lack of data on pharmacokinetics in this population, current guidelines are based on limited scientific rationale [13]. Clear heterogeneity exists between tumor types and clinical protocols (Table 9.1). Weight and age threshold representing the optimal limits for dose reduction are not clearly defined. Most of the time, dose reduction is applied to children under 1 years of age and/or a weight of 10–12 kg [1]. Therefore, in order to avoid unexpected toxicity, an additional dose reduction is recommended in some protocols, despite the fact that body weight-based dosing in infant patients will already represent an effectively reduced dose of around 30% as compared to surface area-based dosing. Therefore, to avoid potential specific toxicity in infants, use of some cytotoxic agents is postponed in younger infants. In most protocols, anthracyclins are avoided in children age <3 months because acute cardiac toxic deaths have been reported [14]. In addition, ifosfamide is omitted in children before age of 1 month to avoid acute renal toxicity. Even if dosage modifications are systematically required, it is rarely done, and newborn and infants

Table 9.1 Chemotherapy dosing modifications in infants proposed according to age/weight in EpSSG (European pediatric Soft Tissue Sarcoma Group), SIOP (International Society of Pediatric Oncology) and other protocols

Protocols	Vincristine	Ifosfamide	D-Actinomycin	Doxorubicin	Etoposide	Carboplatin	Cyclophosphamide	Cisplatin
EpSSG—RMS 2005 study	*From birth to 12 months or <10 kg*: – Dose calculated by BW: 0.05 mg/kg/dose	*No IFO until 1 month* *From 1 to 3 months*: – Dose calculated by BW and then reduced to 50%: 50 mg/kg/dose – If well tolerated, drug dose should be increased by 25–30%/cycle to full dose by BW *From 3 to 12 months or < 10 kg*: – Dose calculated by BW: 100 mg/kg/dose	*From birth to 12 months or <10 kg*: – Dose calculated by body weight: 0.05 mg/kg/dose	*No Doxo until 3 months* *From 3 to 6 months*: – Only for very high risk group *From 6 to 12 months or <10 kg*: – Depending on risk group – Dose calculated by BW: 1 mg/kg/dose				

(continued)

Table 9.1 (continued)

Protocols	Vincristine	Ifosfamide	D-Actinomycin	Doxorubicin	Etoposide	Carboplatin	Cyclophosphamide	Cisplatin
EpSSG—NRSTS 2005 study	*Until 3 months or <5 kg*: – Dose calculated by BW and then reduced to 50%: 0.025 mg/kg/dose – Increased to 0.033 and 0.05 mg/kg/dose at each cycle if well tolerated *From 3 to 6 months or 6–8 kg*: – Dose calculated by BW and then reduced to 33%: 0.033 mg/kg/dose – Increased to 0.04 and 0.05 mg/kg/dose at each cycle if well tolerated *From 6 to 12 months or 8–10 kg*: – Dose calculated by BW: 0.05 mg/kg/dose	*No IFO until 6 months, substituted by cyclophosphamide* *From 6 to 12 months*: – Dose calculated by BW: 100 mg/kg/dose	*Until 3 months or <5 kg*: – Dose calculated by BW and then reduced to 50%: 0.025 mg/kg/dose – Increased to 0.033 and 0.05 mg/kg/dose at each cycle if well tolerated *From 3 to 6 months or 6–8 kg*: – Dose calculated by BW and then reduced to 33%: 0.033 mg/kg/dose – Increased to 0.04 and 0.05 mg/kg/dose at each cycle if well tolerated *From 6 to 12 months or 8–10 kg*: – Dose calculated by BW: 0.05 mg/kg/dose	*No DOXO until 3 months.* *From 3 to 6 months or 6–8 kg*: – Dose calculated by BW then reduced to 33%: 0,65 mg/kg/dose – Increased to 0.8 and 1.25 mg/kg/dose *From 6 to 12 months or 8–10 kg*: – Dose calculated by BW: 1 or 1.25 mg/kg/d (depending of the course)	*From birth to 12 months or <10 kg*: – Dose calculated by BW: 3.3 mg/kg/dose	*From birth to 12 months or <10 kg*: – Dose calculated by BW: 18 mg/kg/dose – Adapted to renal function and blood dosing (AUC)	*From birth to 12 months or <10 kg*: – Dose calculated by BW: 40 mg/kg/dose	

LINES—Neuroblastoma protocol	*Weight < 5 kg*: – Dose calculated by BW and then reduced to 33%: 0.033 mg/kg/dose *Weight 5–10 kg*: – Dose calculated by BW: 0.05 mg/kg/dose			*Weight < 5 kg*: – Dose calculated by BW and then reduced to 33%: 0.67 mg/kg/dose *Weight 5–10 kg*: – Dose calculated by BW: 1 mg/kg/dose	*Weight < 5 kg*: – Dose calculated by BW and then reduced to 33%: 3.3 mg/kg/dose *Weight 5–10 kg*: – Dose calculated by BW: 5 mg/kg/dose	*Weight < 5 kg*: – Dose calculated by BW and then reduced to 33%: 4.4 mg/kg/dose *Weight 5–10 kg*: – Dose calculated by BW: 6.6 mg/kg/dose	*Weight < 5 kg*: – Dose calculated by BW and then reduced to 33%: 3.3 mg/kg/dose *Weight 5–10 kg*: – Dose calculated by BW: 5 mg/kg/dose	
SIOPEL 4—Hepatoblastoma protocol				*Weight < 5 kg*: – Dose calculated by BW and then reduced to 33%: 0.67 mg/kg/dose *Weight 5–10 kg*: – Dose calculated by BW: 1 mg/kg/dose		*Carried out according to renal function with target AUC*		*Weight < 5 kg*: – Dose calculated by BW and then reduced to 33%: 1.8 mg/kg/dose *Weight 5–10 kg*: – Dose calculated by BW: 2.7 mg/kg/dose

BW body weight, *Ifo* ifosfamide, *Doxo* doxorubicin, *EpSSG* European pediatric Soft Tissue Sarcoma Group, *SIOP* International Society of Pediatric Oncology

have to be carefully monitored about clinical and biological consequences of these treatments. Treatment of soft tissue sarcomas (STS) in children, especially rhabdomyosarcoma, is multimodal and the succession of different phases should frequently be adapted to the overall tolerance. Future treatment protocols have to propose pharmacokinetics study in young children to provide novel data on widely used anticancer drugs in infants to improve safety and efficacy of chemotherapy, even for old conventional drugs.

9.4 Infantile Fibrosarcoma

Infantile fibrosarcoma (IFS) is classified in the intermediate (rarely metastasizing) neoplasm occurring during the two first years of life, at a median age of 2–3 months, with 30–50% of diagnoses at birth or in antenatal period. This tumor mainly shows an initial rapid growth, but sometimes presents with indolent evolution. IFS predominantly occur in limbs (66%) or trunk (25%).

Histology could be difficult with a wide morphologic spectrum for this highly cellular neoplasm. Classically, histological patterns include sheets or fascicles of spindle cells or immature round cells, high nuclear/cytoplasmic ratio, focal herringbone pattern of spindle cells and hemangiopericytoma-like vascular pattern with high mitotic activity. Aspects with less cellular areas with collagen bundles (fibromatosis or myofibromatosis-like) could be possible. Immunochemistry is nonspecific with a focal reactivity for smooth muscle actin, muscle-specific actin, and desmin antibodies. Occasional individual cells may stain for cytokeratin, S100 protein, and CD68. IFS is characterized by the recurrent translocation t(12;15)(p13;q25) with the transcript *ETV6-NTRK3*, that is shared by other tumors as mainly hypercellular mesoblastic nephroma, MASC salivary gland carcinoma, and secretory breast cancer. Therefore, in addition to standard immunochemistry histological examination, *ETV6-NTRK3* fusion transcript or similar transcript involving *NRTK* fusion partners should be systematically assessed (FISH, RT-PCR, or genomic sequencing). In its absence, other diagnosis should be discussed.

Distant metastases are rare and the prognosis is favorable in the majority of cases. The main concern is local spreading of the tumor often infiltrating neurovascular structures. Primary surgery should only be considered at diagnosis in small tumors that can be completely resected without any functional consequences, if there is no clear clinical evidence of lymph node or metastatic disease. In case of complete surgery or microscopic residue (IRS Group I or II, i.e., complete resection or microscopic residue) of a localized tumor, no further treatment is needed. Large mutilating initial surgery must be avoided. In case of initial inoperability (IRS-III group), neoadjuvant chemotherapy should be delivered and conservative delayed surgery should be considered after tumor reduction with chemotherapy. Delayed surgery should, as a rule, also be conservative [7]. IFS are chemosensitive tumors with major response to chemotherapy in approximately 2/3 of patients. Chemotherapy must be administered when conservative complete tumor resection is not possible at

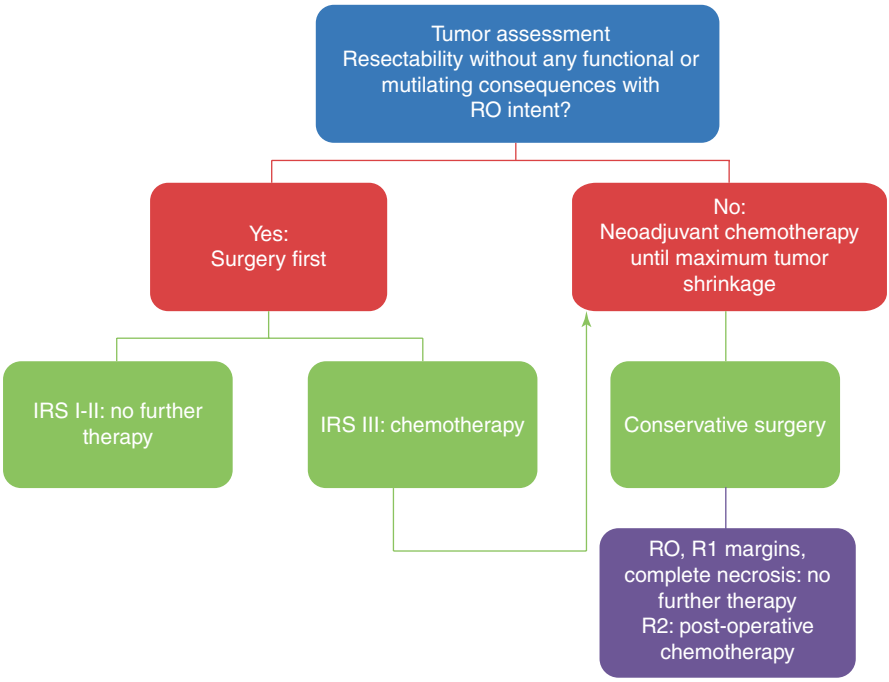

Fig. 9.3 Overall EpSSG strategy for infantile fibrosarcoma. Abbreviations: *IRS I* complete resection, *IRS I* microscopic residue, *IRS III* macroscopic residue, *R0* complete delayed surgery, *R1* microscopic incomplete delayed surgery, *R2* macroscopic incomplete delayed surgery

diagnosis. Main aim of chemotherapy is to reduce the tumor to allow delayed non-mutilating tumor resection. Response to chemotherapy can be slow (until several months) and failure to chemotherapy should only be discussed in case of tumor increased (> 25% volume increase) or in the absence of tumor reduction after at least 3 months of therapy. In consideration of the age of patients and existing literature, data regimens without alkylating or anthracyclin agents should be chosen as initial treatment. Therefore, the European pediatric Soft Tissue Sarcoma Group (EpSSG) proposal recommends the VA regimen (vincristine-actinomycin-D) as preferred initial regimen (Fig. 9.3) [7]. Chemotherapy should be continued until surgery, and stopped after tumor resection. In case of complete clinical and imaging (RMI) remission after neoadjuvant chemotherapy, if patient can be strictly followed, delayed surgery can be avoided. If the response is not sufficient to permit a conservative surgery but initialtumour shrinkage appears evident after several months, ifosfamide could be added (IVA regimen) or cyclophosphamide with doxorubicin (CadO or VAC regimen). With this conservative strategy, overall prognosis is good with a 3 year-event free and overall survivals of 84.0% and 94.0% respectively [7]. There are recent evidences that new targeted agents acting at the *ETV6-NTRK3* fusion level may be really active against IFS [15]. These agents should be considered in unresectable cases when there is no evidence of response to chemotherapy

and impossible conservative surgery (larotrectinib or other targeted therapy as lestaurtinib, crizotinib and entrectinib). Drug available in an oral solution (larotrectinib) is necessary at this age.

9.5 Soft Tissue Rhabdoid Tumor

Initially described as atypical variants of Wilms tumors, malignant rhabdoid tumors can arise either from central nervous system (called Atypical Teratoid/Rhabdoid Tumors, AT/RTs) or from any extracranial tissue or organ. Soft tissues are the third location after central nervous system and kidney. Rhabdoid tumors are rare diseases; its incidence was estimated in 2010 in United Kingdom around 0.6 per million children a year. With a median age at diagnosis of 1.4 year old, onsets is commonly before 5 years old and between 40 and 60% of cases arise during the first year of life or prenatal period.

Soft tissue rhabdoid tumors typically present as a rapidly growing mass from any subcutaneous but also profound location such as paravertebral tissues (Fig. 9.1). When tumor develops during prenatal period, it can be discovered during prenatal examination or at birth. Compression of organs, vessels, peripheral nerves or spinal cord, or regional lymph nodes involvement can be the only clinical features at diagnosis [16]. Initial radiological assessment is adapted following location with CT-scan and/or magnetic resonance imaging (MRI), and should determine precise primary site and proximity of normal structures. Surgical or radio-guided biopsy allows histopathological diagnosis. Typical rhabdoid features are large polygonal cells, intracytoplasmic eosinophilic inclusions, and uncondensed chromatin with prominent nucleus (Fig. 9.4). Association of a rhabdoid phenotype with a complete loss of expression with immunohistochemistry of *SMARCB1* (also called *INI1/BAF47/SNF5*), or *SMARCA4* (*BRG1/BAF190/SNF2*) in <10% of cases, is neces-

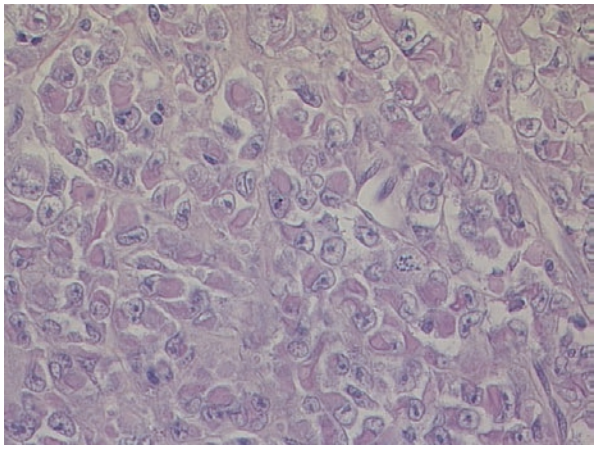

Fig. 9.4 Pathology aspect of a rhabdoid tumor with classical rhabdoid features including large polygonal cells, intracytoplasmic eosinophilic inclusions, and uncondensed chromatin with prominent nucleus (coloration hematoxylin-eosin-safran coloration [HES]) (*Courtesy Dr P Freneaux*)

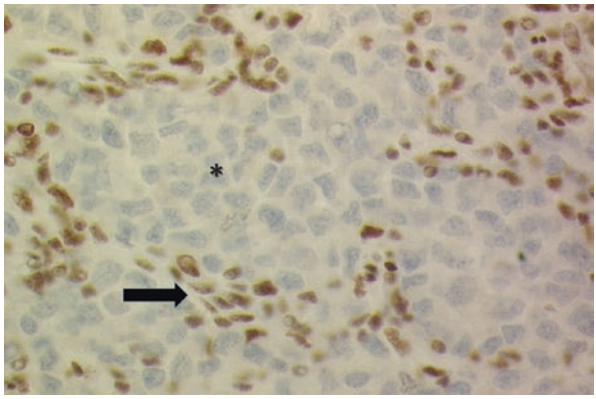

Fig. 9.5 Rhabdoid tumor features with INI 1 immunohistochemistry showing a loss of INI 1 expression in the blue rhabdoid tumors cells (∗) with a preserve cytoplasmic staining in endothelial cells within normal blood vessels ((→), internal positive control) (*Courtesy Dr P Freneaux*)

sary to confirm the diagnosis (Fig. 9.5). Disease extension will be assessed by thoracic and abdominal imaging, brain MRI and ^{99m}Tc bone scan. Stage will be defined like others pediatric soft tissue sarcomas both with TNM pre-operative staging classification, and IRS post-operative one. Molecular characterization of tumor genomic events leading to *SMARCB1* biallelic inactivation will confirm diagnosis at molecular level and guide germline explorations [17]. Indeed, heterozygous *SMARCB1* mutation is found in 15–30% of cases at germline level, associated with an increased risk of plurifocal tumors, a younger age at onset and a poorer prognosis [18, 19].

Global strategy for treatment is based on intensive conventional multi-agent chemotherapy adapted to the young age of patients, surgery and radiotherapy if possible. Refractory disease to initial chemotherapy or early relapse under treatment is frequent situations, with a median time to progression of 5 months. Then, local treatment must be considered early in the treatment schedule. Possibility of local irradiation has been recognized as an independent prognosis factor, and should be given early after surgery whatever possible butextension of disease at diagnosis and late effects of this therapy in young patients limits their indications. Although high dose chemotherapy followed by autologous stem cell transplantation is well reported in AT/RTs, its role remains controversial for extracranial tumors.

Despite intensive treatment protocols, global prognosis of extracranial rhabdoid tumors remains poor with a 5 years overall survival <40%. Considering patients under 12 months old at diagnosis, prognosis is worse with a 20% 4 years overall survival. Long term side effects for patients in remission is a great matter of concern in this context of intensive multimodal treatment for very young children, in particular second neoplasms, renal impairment or local growth impairment in the irradiation field.

With a well-established stable genome apart from *SMARCB1* inactivation, biology of RTs is dominated by the role of this tumor suppressor gene. SMARCB1 protein is a core member of the SWI/SNF complex, which participate to the regulation of gene expression by controlling chromatin compaction and so accessibility to transcription machinery [20]. On other hand, antagonist role between *SMARCB1*

and polycomb complex PRC2 suggests that loss of *SMARCB1* will impair gene expression regulation also by EZH2 dependent histone modifications, catalytic subunit of PRC2. Then, deregulation of epigenetic control of gene expression is considered to be a hallmark of rhabdoid tumors. Epidrugs are currently under preclinical or clinical investigations, restoring epigenetic control of cell homeostasis, particularly EZH2 inhibitors actually in phase I/II international clinical trials [21].

9.6 Infant and Newborns RMS

Rhabdomyosarcoma (RMS) is the most common soft tissue tumour in childhood. It comprises less than one-third of soft tissue sarcoma occurring in the first year of life and 5–8% of all malignant tumours [1, 14, 22, 23]. In the very young, RMS represents a fascinating and difficult medical challenge due to i) the an important heterogeneity within neonatal RMS presentations, some tumours being very aggressive and resistant to chemotherapy while others are chemosensitive and easily cured, and ii) the physiologic immaturity of various organs in infants is responsible for the different metabolism of drugs compared to older patients and potential vulnerability to acute and late effects of therapy, particularly radiotherapy and alkylating agent.

Genetic counseling should be considered if RMS occurred in newborn/infant especially in case of family history of cancer, dysmorphology/congenital malformation, and specific histology subtypes such as pleiomorphic or anaplastic RMS, and multifocal locations. Indeed, several genetic predisposition syndromes have been associated with RMS and index cases usually develop RMS in the first years of age. The most frequent is Li-Fraumeni syndrome, but others like type 1 neurofibromatosis (pelvic RMS), Beckwith-Wiedemann syndrome, *DICER1* syndrome mainly (pelvic RMS in female), and RASopathies should also be raised.

Clinical presentation is often non-specific with a growing tumour masse in the primary tumour location. Swelling, pain (not frequent), and clinical impacts of the masse are reported by the parents: loss of appetite for abdominal tumours, vaginal or urinary bleeding, nerve palsy, or others. As for other soft tissue tumours in neonates, the tumour may grow very fast and have life-threating consequences requiring urgent diagnosis and treatment. Unlike RMS occurring in the older, the most frequent primary tumour location is the bladder/prostate (30%) area followed by non-parameningeal head and neck (20%) site. Classic but exceptional, is the "blueberry muffin baby" with cutaneous manifestation that presents as non-blanching, blue-red macules or firm, dome-shaped papules, and associated with neoplastic lesions of the skin revealing alveolar RMS. Complete initial work-up should include, in addition of careful and age-adapted primary tumour imaging, thoracic CT scan or MRI, bone marrow aspirates, and bone scintigraphy. Less than 20% are metastatic at diagnosis, predominantly in the lung, and 15% present node positive disease.

Major subtypes of RMS include alveolar (aRMS) and embryonal (eRMS) tumours. Whereas aRMS typically contain translocations generating *PAX3-FOXO1* or *PAX7-FOXO1* fusions that block terminal myogenic differentiation, no functionally comparable genetic event has been found in eRMS, except a rare myogenic transcription factor *MYOD1* mutation identified in a subset of more aggressive

eRMS. Rarely some other forms are encountered, like spindle cell tumour or sclerosing RMS (S/ScRMS), often regarded as atypical embryonic forms. These S/ScRMS appears to be over-represented in congenital presentations, involve mostly the paratesticular and the head and neck region, and associated with a more favourable outcome [24]. In a series of 45 French RMS infants, the respective frequency of eRMS, aRMS, and S/ScRMS were 49%, 20%, and 31%, respectively (personal communication) [25]. Identification of specific genetic alterations, which can be used as diagnostic markers in daily practice, has always been a great challenge and allowed to develop a panel of molecular tools dedicated to the detection to each kind of aberration (Fig. 9.6). Recently, molecular rearrangement involving *NCOA2* or *VGGL2* genes have been described in some infants with S/ScRMS [26, 27]. These *NCOA2*- or *VGLL2*-associated RMS seemed to present more favourable outcomes, with no metastatic spread described, although a small numbers of cases and short follow-up have been reported.

As the majority of clinical trials does not include infants <6 months, heterogeneous and tailored therapies are common in the main reported series. At diagnosis, primary excision (± after initial biopsy, depending of tumour size and location, to be discussed in a multidisciplinary board before surgery) is attempted when complete and conservative resection is considered feasible. Otherwise, a biopsy was taken and neo-adjuvant chemotherapy administrated, in order to shrink the tumour and prevent metastases. Second look surgery is performed to achieve complete remission if necessary. Careful attention should be made with chemotherapy drugs, doses, and schedules (see specific chapter). It is recognized that external beam radiotherapy (photon or proton) should not be delivered in children <1 year. Therefore, when indicated, brachytherapy should be encouraged, especially in genitourinary RMS, to limit late sequelae.

Survival varies in largest series between 60 and 80%. Infants <1 year with RMS appear to have worse outcomes than older patients, in part because of high rates of local failure probably due to reluctance to use aggressive local control measures in infant. Other well-known prognostic factors in RMS include tumour size and site, histology and FOXO1 fusion status, TNM status and quality of initial resection.

RMS is the most common soft tissue in newborns and infants. Age-adapted initial work-up and biopsy, treatment strategy, and chemotherapy are crucial as well as careful supportive care. The challenge for the future will be to better characterize biological subtests, while integrating other known prognostic factors, to adapt treatment strategy at this specific age.

9.7 Fibroblastic: Myofibroblastic Tumors and Intermediate Tumors

Fibroblastic and myofibroblastic tumors account for 12% of all pediatric soft tissue tumors. Some of them occur more specifically in neonates and infants. Their diagnosis may be delicate due to their heterogeneity, their rare incidence, clinical and morphological overlapping features between benign and malignant tumors. Thus clinical and histological correlation remains crucial taken into account location of

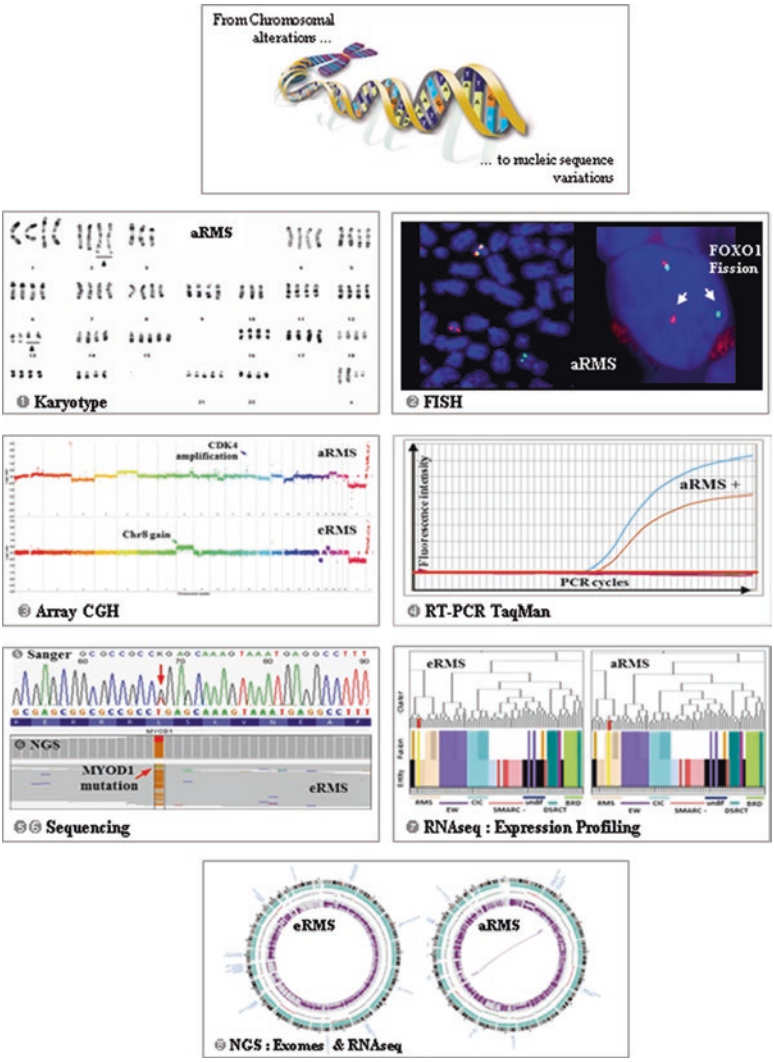

Fig. 9.6 Rhabdomyosarcomas characterization, from cytogenetics to molecular biology: Identification of specific genetic alterations, which can be used as diagnostic markers in daily practice, has always been a great challenge and allowed to develop a panel of molecular tools dedicated to the detection to each kind of aberration. Examples of these technical evolutions integrating pathology/genetic alteration/technics are illustrated above. The specific PAX3-FOXO1 translocation involved in alveolar Rhabdomyosarcoma (aRMS) is shown on a (1) classical karyotype; Fission of FOXO1 locus can also be visualized by (2) FISH either on metaphases (left panel), or interphases; Specific amplifications, like CDK4, are often observed in aRMS whereas gains of whole chromosome 8 are more common in embryonal Rhabdomyosarcoma (eRMS), both alterations are easily highlight by (3) aCGH; *PAX3/7-FKHR* fusion transcript can be identified by (4) Real Time RT-QPCR; Sequencing either by (5) classic Sanger method or by (6) Next Generation Sequencing (NGS) allow to detect specific MYOD1 mutation (p.L122R). Expression data obtained by (7) RNAseq reveal very specific pattern for both subtypes. Finally realization of (8) Whole Exome Sequencing (WES) and RNAseq offer an integrative molecular snapshot where these different kinds of alterations (Fusion, Amplifications, Gains, Mutation, Expression profiles) can be assessed simultaneously

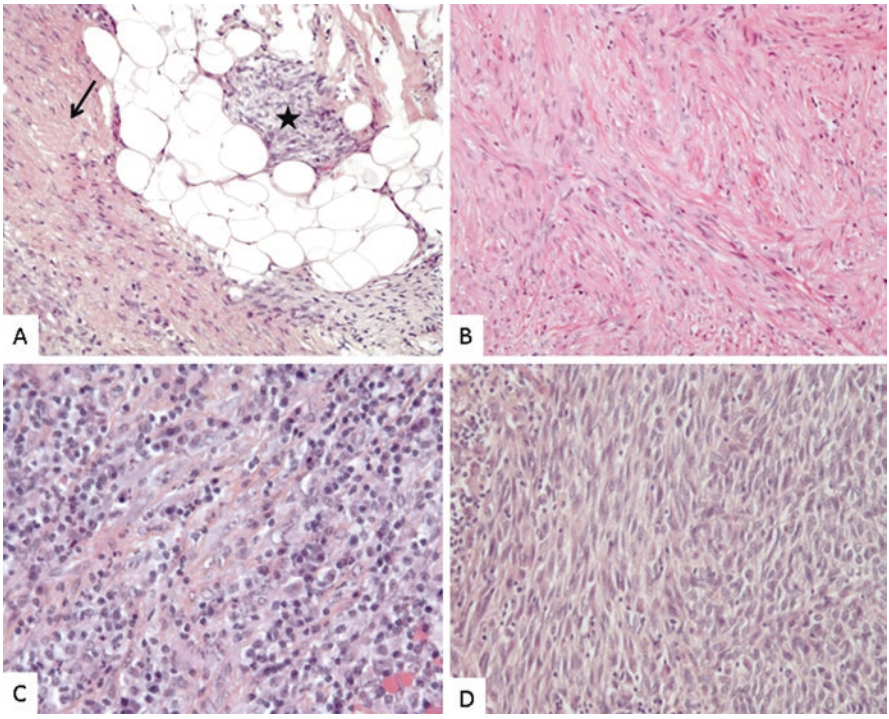

Fig. 9.7 (**a**) Fibrous hamartoma of infancy: association of immature basophilic mesenchymal tissue (star), fibrous septa (arrow) and mature adipocytes. (**b**) Infantile myofibroma: whorled bundles of spindle cells with eosinophilic cytoplasm. (**c**) Inflammatory myofibroblastic tumor: myofibroblastic spindle cell proliferation with prominent mixed inflammatory infiltrate. (**d**) Infantile fibrosarcoma: highly cellular spindle cell proliferation with herringbone pattern

the disease, timing of occurrence (congenital or delayed formation), uni or multifocality … Main histological types in neonates and infant encompass juvenile fibromatosis (infantile myofibroma/myofibromatosis, fibrous hamartoma of infancy, lipofibromatosis, and hyaline fibromatosis of juvenile type), inflammatory myofibroblastic tumor and infantile fibrosarcoma (Fig. 9.7). In routine practice, considering the age of the patient and sharing diagnosis with expert pathologists are crucial to achieve correct diagnosis of soft tissue tumors in infants. An increasing number of genetic alterations are described, sometimes shared with other pediatric or adult tumors (i.e. *SRF-RELA* fusion which recently define a novel subset of cellular myofibroma/myopericytoma that can mimic sarcomas [28]), with sometimes unknown physiopathological signification.

Infantile myofibroma/myofibromatosis may present as solitary, multicentric or generalized (with visceral involvementand thereforeworse prognosis) disease. Solitary and multicentric myofibromas are the most common subtypes and present as isolated or multiple nodules in the skin, soft tissues, and bones, especially in head and neck, trunk and extremities. Histology shows whorled bundles of spindle cells with eosinophilic cytoplasm, oval nuclei with fine chromatin and inconspicuous nucleoli. Vascular pattern can be hemangiopericytoma-like. Zonal pattern with

varying cellularity is usually observed. Periphery typically shows intraluminal budding of lesion into vessels. Necrosis and mitotic activity have no prognostic significance. Immunohistochemistry shows staining by smooth muscle actin, desmin (variable staining) whereas CD34 only decorate vascular web. No genetic abnormality has been reported in sporadic « classical » infantile myofibroma. In familial infantile myofibromatosis, patients may present with *PDGFR-β* gain-of-function mutations [29, 30]. Treatment consists of surgical resection but spontaneous regression has been reported. In multifocal lesions, efficacy of low dose chemotherapy has been reported (methotrexate-vinblastine) [31]. Chemotherapy is therefore delivered in the absence of spontaneous regression during follow-up or in life/function threatening situations.

Fibrous hamartoma of infancy is congenital in 20% of cases. Male predominance is reported. It usually presents as a solitary subcutaneous mass in axillary and inguinal regions, upper arms, upper trunk or external genitalia, with poorly demarcated limits. This lesion is typically histologically made of three components: immature basophilic mesenchymal tissue made of fascicules of stellate cells, mature fibrous septa positive for smooth muscle actin, and islands of mature adipose tissue expressing S100 protein. Recently, *EGFR* exon 20 insertion/duplication mutations have been described [28]. Fibrous hamartoma of infancy is cured by surgical excision despite possible recurrence.

Lipofibromatosis is often congenital (25% of cases) and involves mainly distal extremities, less often trunk and head and neck with mainly infiltrative tumor. This poorly demarcated lesion is made of mature adipose tissue intermingled with fascicles of fibroblasts among variable collagen and focal myxoid change. Immunoreactivity for smooth muscle actin and CD34 is variable in spindle cells and S100 protein in adipose tissue. No staining is detected with myogenin. However diagnosis may be challenging due to lack of specificity of these histological criteria and no known molecular abnormalities. Lipofibromatosis may be heterogeneous, encompassing different entities. Surgical resection is performed in lipofibromatosis but remains often incomplete in this infiltrative lesion.

Hyaline fibromatosis of juvenile type is a rare autosomal recessive disorder leading to development of nodular and papular cutaneous lesions on the hand, scalp, ears, and nose. Infantile systemic hyalinosis is the most severe form, associated with visceral involvement and death in early childhood. Histology shows nodular proliferations of spindle cells arranged in fascicles and abundant eosinophilic matrix. Older lesions are less cellular. This disease is due to mutations in the capillary morphogenesis gene 2 (*CMG2*) in both juvenile and infantile forms. Diagnosis can be performed by the association of histologically prominent hyaline material, clinical abnormalities, and presence of the mutation.

Inflammatory myofibroblastic tumor (IMT) occurs at all age especially children and young adult. Inflammatory clinical syndrome is detected in 1/3 of cases. IMT usually develop in viscera (lungs, abdomen, retroperitoneal and pelvic sites) but also in the extremity soft tissues, head and neck, and central nervous system. IMT are part of tumors of intermediate biological potential as they rarely metastasize and have significant local recurrence potential. Histology typically shows myofibroblastic spindle cell proliferation with prominent mixed inflammatory infiltrate.

Myofibroblastic cells may be plump with eosinophilic or amphophilic cytoplasm. Cellularity is variable as growth patterns associating sometimes myxoid, cellular spindle and collagenized patterns. Inflammatory infiltrate often encompass plasma cells, lymphocytes, and eosinophils. Mitotic activity is low. Immunohistochemistry shows variable staining of myofibroblasts for smooth muscle actin and desmin. In 50% of cases, a clonal rearrangement of chromosome 2p23 involving the anaplastic lymphoma kinase (*ALK*) gene, leading to hyperexpression of *ALK* in tumor tissue. This hyperexpression is detectable by immunostaining against ALK-1 and mutation could be assessed by RT-PCR. Numerous fusion partners have been so far described. ALK-negative IMT may present rearrangement involving *ROS1* or *PDGFR*-β. These data tend to show critical role of receptor tyrosine kinase hyperactivation in the biology of IMT and open the field for development of targeted medical treatment. In routine practice, differential diagnosis of IMT, especially *ALK* negative IMT, remains sometimes challenging. Main treatment is tumor resection if possible. In metastatic lesion or unresectable tumors, medical drugs should be discussed (steroid, low dose chemotherapy, target therapies against *ALK*).

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