Histol Histopathol (2021) 36: 3-18

http://www.hh.um.es

Histology and Histopathology
From Cell Biology to Tissue Engineering

REVIEW **Open Access**

Angiosarcomas: histology, immunohistochemistry and molecular insights with implications for differential diagnosis

Isidro Machado[1,2], Francisco Giner[3], Javier Lavernia[4], Julia Cruz[1], Víctor Traves[1], Celia Requena[5], Beatriz Llombart[5], José Antonio López-Guerrero[6,7,8] and Antonio Llombart-Bosch[9]

[1]Pathology Department, Instituto Valenciano de Oncología, [2]Pathology Department, Hospital Quirón, [3]Pathology Department, University Hospital La Fe, [4]Department of Oncology, Instituto Valenciano de Oncología, [5]Dermatology Department, Instituto Valenciano de Oncología, [6]Laboratory of Molecular Biology, Instituto Valenciano de Oncología, [7]IVO-CIPF Joint Research Unit of Cancer, Príncipe Felipe Research Center (CIPF), [8]Department of Pathology, School of Medicine, Catholic University of Valencia 'San Vicente Mártir' and [9]Pathology Department, University of Valencia, Valencia, Spain

Summary. Angiosarcomas (AS) represent a heterogenous group of tumors with variable clinical presentation. AS share an important morphologic and immunohistochemical overlap with other sarcomas, hence the differential diagnosis is challenging, especially in poorly-differentiated tumors. Although molecular studies provide significant clues, especially in the differential diagnosis with other vascular neoplasms, a thorough hematoxylin and eosin analysis remains an essential tool in AS diagnosis. In this review, we discuss pathological and molecular insights with emphasis on implications for differential diagnosis in cutaneous, breast, soft tissue and visceral AS.

Key words: Angiosarcomas, Immunohistochemistry, Molecular biology, Differential diagnosis

Introduction

Angiosarcoma (AS) is a rare but highly aggressive vasoformative sarcoma characterized by high rates of recurrence and tumor-related death (Naka et al., 1995; Mark et al., 1996; Fury et al., 2005; Fayette et al., 2007; Abraham et al., 2007; Young et al., 2010; Buehler et al., 2014; Wang et al., 2017a,b; Zhang et al., 2019; Painter et al., 2020; Weidema et al., 2019a,b, 2020). Survival for AS patients is generally poor, with reported five-year survival rates of around 40% and close to 15% in metastatic tumors (Buehler et al., 2014; Weidema et al., 2019a,b, 2020). AS prognosis may be influenced by clinical and pathological factors and histological high grade is related with poor prognosis (Fury et al., 2005; Abraham et al., 2007; Buehler et al., 2014; Lee et al., 2019; Weidema et al., 2019a,b, 2020). Depending on previous treatment (radiotherapy or systemic treatment), the mainstay of localized AS therapy consists of surgery with adjuvant radiotherapy and/or doxorubicin-based or taxane single-agent chemotherapy (Abraham et al., 2007; Hoang et al., 2018; Lodhi et al., 2018; Florou et al., 2019; Painter et al., 2020). For locally advanced disease, without local treatment options or metastatic disease, the best choice is systemic treatment within clinical trials (Pasquier et al., 2016). Although recent advances in oncology, such as targeted therapy and immunotherapy may have benefited some AS patients, a more precise role for these new treatment options remains unclear (Fujii et al., 2014; Honda et al., 2016; Shimizu et al., 2016; Botti et al., 2017; Shinhu et al., 2017; D'Angelo et al., 2018; Wolina, 2018; Florou et al., 2019).

In this review, we discuss pathological and molecular insights focussing on implications for differential diagnosis.

A wider spectrum of clinical presentation in Angiosarcomas

AS can occur in any organ or tissue, either as a primary AS or as a secondary AS linked to lymphedema or external damaging factors (radiation therapy or vinyl chloride exposure). In addition, AS have also been reported in association with other neoplasms (malignant peripheral nerve sheath tumor, germ cell tumor or schwannoma) (Hunt and Santa Cruz, 2004; Carpino et al., 2005; Fury et al., 2005; Antonescu, 2014; Matoso

Corresponding Author: Isidro Machado, Pathology Department, Instituto Valenciano de Oncología, Valencia, Spain. e-mail: Isidro.Machado@uv.es

DOI: 10.14670/HH-18-246

and Epstein, 2015; Baker and Schnitt, 2017; Ginter et al., 2017; Leduc et al., 2017; Requena et al., 2017; Shustef et al., 2017; van IJzendoorn et al., 2017; Gourley et al., 2018; Ishida et al., 2018; Ginter et al., 2019; Abdou et al., 2019; Alves and Rimola, 2019; Singh et al., 2019; Weiss and Goldblum, 2019; Wilson et al., 2019; Yasir and Torbenson, 2019; Pazhenkotill and Bode, 2020) or associated with foreign bodies (vascular grafts, prosthetic material) (Agaimy et al., 2016). The association between UV light exposure and AS is under debate (Requena et al., 2017; Shon and Billings, 2017; Shustef et al., 2017; Ishida et al., 2018).

The most frequent locations of AS include skin (especially the head and neck area), soft tissue and breast, whereas it is less common in liver, spleen, heart and bone (Ginter et al., 2019; Abdou et al., 2019; Alves and Rimola, 2019; Singh et al., 2019; Weiss and Goldblum, 2019; Wilson et al., 2019; Yasir and Torbenson, 2019; Pazhenkotill and Bode, 2020). Therefore, depending on the primary site, AS can be divided into cutaneous, breast, soft tissue or visceral (Fig. 1A-F). The majority of secondary AS are cutaneous, although rare cases have been reported in deeper-seated tissues (Seo and Mink, 2003; Weaber and Willings, 2009; Mentzel et al., 2012; Doyle, 2014; Ginter et al., 2014; Abdou et al., 2019; Habeed and Rubin, 2019; Lesluyes et al., 2019; Taffurelli et al., 2019). Clinically, secondary AS related to radiation are frequently located in breast areas in female patients (Backer and Schnitt, 2017; Abdou et al., 2019; Corradini et al., 2020) while primary cutaneous AS of the head and neck region occurs mainly in elderly men (Pawlik et al., 2013; Ishida et al., 2018; Lee et al., 2019).

Cutaneous angiosarcoma may initially appear as a bruise, or a raised purplish-red papule, it is typically multifocal and can be mistaken for a simple benign lesion such an ecchymoses or cellulitis, leading to delayed diagnosis (Requena et al., 2017; Shon and Billings, 2017; Shustef et al., 2017; Ishida et al., 2018). As tumor size increases, tissue infiltration, oedema, tumor fungation (Fig. 1), ulceration, and haemorrhage may develop (Requena et al., 2017). Deeper soft tissue and visceral lesions present as an expanding mass associated with pain or discomfort (Leduc et al., 2017; Ginter et al., 2019; Abdou et al., 2019; Alves and Rimola, 2019; Singh et al., 2019; Weiss and Goldblum, 2019; Wilson et al., 2019; Yasir and Torbenson, 2019). Breast AS secondary to radiotherapy are usually superficial (dermis and subcutis), while primary AS of breast are usually intraparenchymal and appear in young women (Baker and Schnitt 2017; Abdou et al., 2019; Beca et al., 2020; Corradini et al., 2020).

Hematogenous spread is frequent in AS, with the lungs presenting as the most common site for metastatic disease, where it may occur as pleural disease, haemorrhagic pleural effusion, or pneumothorax.

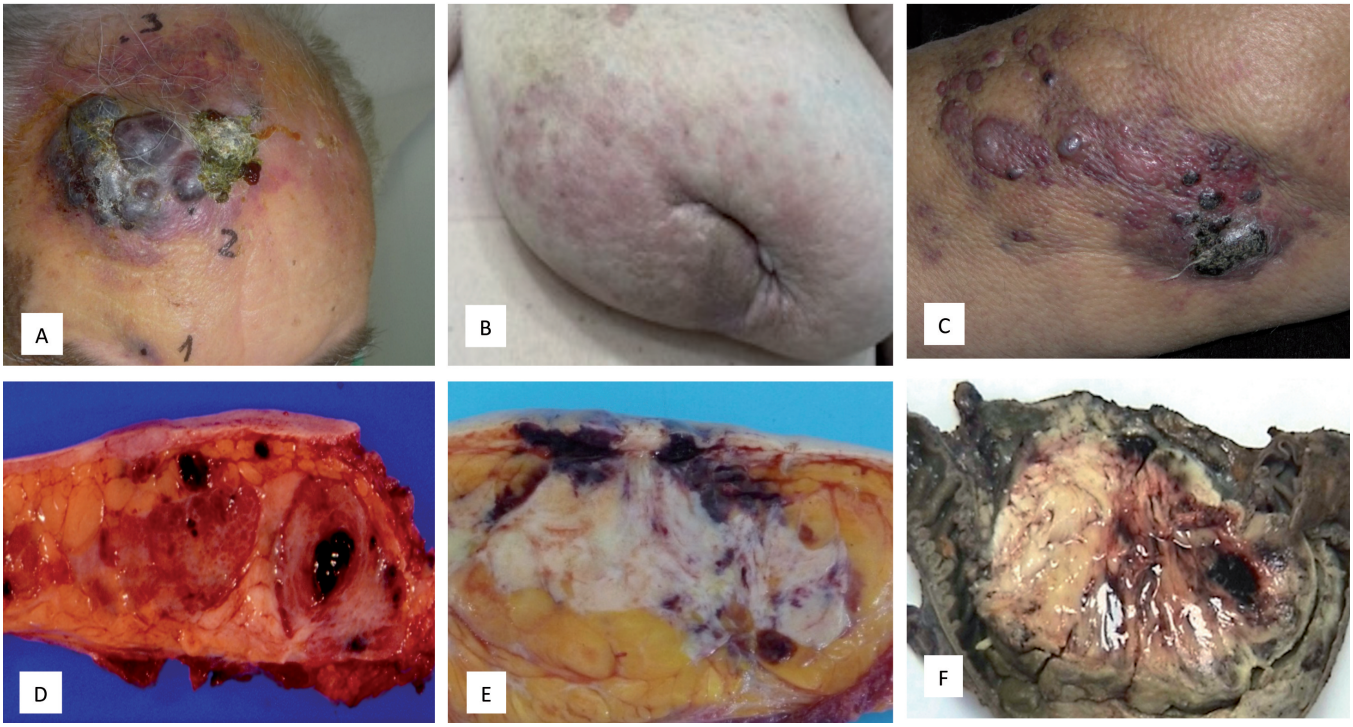

Fig. 1. Clinical and grossly detail in AS. **A.** Primary Angiosarcoma from scalp (AS). **B.** Secondary breast AS (post-radiation). **C.** Secondary cutaneous AS (lymphedema-related). **D.** Primary breast AS. **E.** Secondary mammary AS (post-radiation). **F.** Primary intestinal AS.

Histopathology in angiosarcomas: from well-differentiated subtypes to undifferentiated and unrecognizable tumors

Histologically, AS displays a wide range of appearances, ranging from well-formed vascular spaces with minimal cytologic atypia (Fig. 2A,B) which resemble hemangiomas, to poorly-differentiated tumors with solid sheets of spindled (Fig. 2C), epithelioid (Fig. 2D), round, or anaplastic cells (Fig. 2F) that lack evident vascular structures (Hunt and Santa Cruz, 2004; Antonescu, 2014; Doyle, 2014; Baker and Schnitt, 2017; Shon and Billings, 2017; Alves and Rimola, 2019; Weis and Goldblum, 2019; Jung et al., 2020; Papke and Hornick, 2020). This varied spectrum of morphological appearance complicates the differential diagnosis.

Secondary AS, especially those related to radiation, are frequently located in the dermis (Fig. 2A). Several anastomosing and dissecting vascular channels are observed under hematoxylin and eosin (H&E) examination. In fact, the histopathology of cutaneous well-differentiated AS is not dissimilar to post-radiation atypical vascular proliferation (PRAVP) (Hunt and Santa Cruz, 2004; Guo et al., 2011; Mentzel et al., 2012; Ginter et al., 2014; Backer and Schnitt, 2017; Requena et al., 2017). PRAVP refers to a small, usually lymphatic-type vascular proliferation (Fig. 2C) and although most atypical vascular lesions pursue a benign course, they may recur (Weaver and Billings, 2009; Mentzel et al., 2012; Wick, 2016; Requena et al., 2017). The option of classifying PRAVP as a precursor lesion of AS is still under debate. In both lesions (cutaneous well-differentiated AS and PRAVP) the neoplastic cells lining the vascular channel exhibit hyperchromatic and irregular nuclei with variable nuclear atypia, while mitotic figures or necrosis are infrequent (Hunt and Santa Cruz, 2004; Guo et al., 2011; Mentzel et al., 2012; Ginter et al., 2014; Backer and Schnitt, 2017; Requena et al., 2017). The differential diagnosis between PRAVP and AS is described in section 6. The non-well-differentiated AS may display poorly-differentiated areas (Fig. 2D-F) leading to occasional misdiagnosis of high-grade AS, either when focal vascular differentiation cannot be clearly distinguished or where immunohistochemical results are inconclusive. In visceral location, for instance the liver, AS may present several histological patterns, including vasoformative, epithelioid or spindled cell morphology and sinusoidal or peliotic growth, with the last two being more difficult to recognize (Alves and Rimola, 2019; Wilson et al., 2019; Yasir and Torbenson, 2019; Zeng et al., 2020).

Immunohistochemistry and electron microscopy may support the histological diagnosis of AS, while either neuroendocrine or epithelial differentiation are not exceptional in AS

In several scenarios immunoreactivity for vascular markers will confirm the histological diagnosis of AS (Fernandez et al., 2012; Fisher, 2013; Ginter et al., 2014;

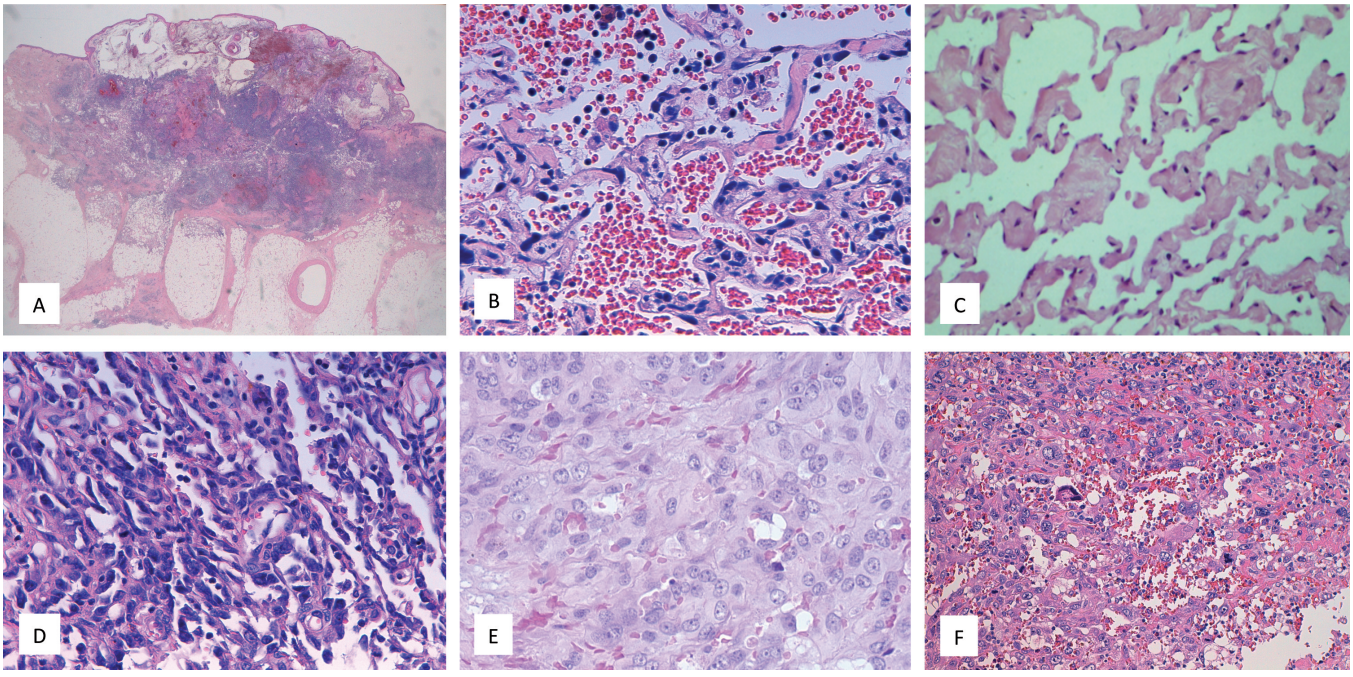

Fig. 2. AS histological spectrum. **A.** Secondary cutaneous AS with dermal and subcutaneous infiltration, hematoxylin and eosin (H&E). **B.** Vasoformative, well-differentiated cutaneous AS, H&E. **C.** Post-radiation atypical vascular proliferation, H&E. **D.** Solid and spindle cell secondary AS, H&E. **E.** soft tissue epithelioid AS, H&E. **F.** Testicular AS with pleomorphic anaplastic cells, H&E. A, x 10; B, D, E, x 40; C, F, x 20.

Wang et al., 2017a,b; Subramaniam et al., 2018; Corradini et al., 2020; Di Battista et al., 2020; Papke and Hornick, 2020). A combination of CD31 (Fig. 3A), CD34, D2-40 (Fig. 3C), VE-cadherin, VEGFR (1, 2, and 3) are frequently used as an appropriate tool in AS diagnosis, however cytoplasmic immunoreactivity of these antibodies may occasionally demonstrate an inconsistent staining background (Fisher, 2013; Antonescu, 2014; Backer and Schnitt, 2017; Wang et al., 2017a,b). Strong and nuclear immunopositivity for ERG or FLI1 (Fig. 3B) can aid interpretation of the above-mentioned antibodies, which is sometimes problematic (Hunt and Santa Cruz, 2004; Ko and Billings, 2015; Machado et al., 2018; Kuhn et al., 2019). Vascular markers have the advantage that they stain the endothelial cells of any tissue, thus they can be used as positive internal control, indicative of tissue quality, especially in poorly-fixed tissue (Hunt and Santa Cruz, 2004; Antonescu, 2014; Marusic and Billings, 2017; Machado et al., 2018).

An important observation is that vascular markers, both for nuclear or cytoplasmic and membranous

Table 1. Antibodies, source, dilution and conditions of vascular markers in angiosarcoma.

Antibodies	Source	Clone	Dilution	Pretreatment condition	Staining pattern
CD31	DAKO M0823	JC70A	1/50	Autoclave, Low Ph	M, C
CD34	DAKO M7165	QBEnd-10	1/50	Autoclave, Low Ph	M
D2-40	DAKO IR072	D2-40	Prediluted	PTLINK High Ph	M, C
ERG	DAKO IR659	EP-111	Prediluted	Autoclave, High Ph	N
Fli1	MASTER DIAGNOSTIC MAD-210407-Q	MRQ1	1/40	Autoclave, High Ph	N
VE-Cadherin	SANTA CRUZ BIOTECHNOLOGY SC-6458	POLYCLONAL	1/50	Autoclave, Low Ph	C
VEGF	NEOMARKERS	Mab MS-1467-P	1/50	Autoclave, High Ph	M,C
VEGFR1 (FLT-1)	SANTA CRUZ BIOTECHNOLOGY SC-316	POLYCLONAL	1/400	Autoclave, Low Ph	M,C
VEGRF2 (FLK-1)	SANTA CRUZ BIOTECHNOLOGY SC-315	POLYCLONAL	1/400	Autoclave, Low Ph	M,C
VEGR3 (FLT-4)	SANTA CRUZ BIOTECHNOLOGY SC-321	POLYCLONAL	1/400	Autoclave, Low Ph	M,C
MYC	(ROCHE) VENTANA N° CAT 790-4628	RABBIT MONOCLONAL Y69	Prediluted	Cell Conditioning Solution (CC1)	N

N, nuclear; C, cytoplasmic; M, membranous.

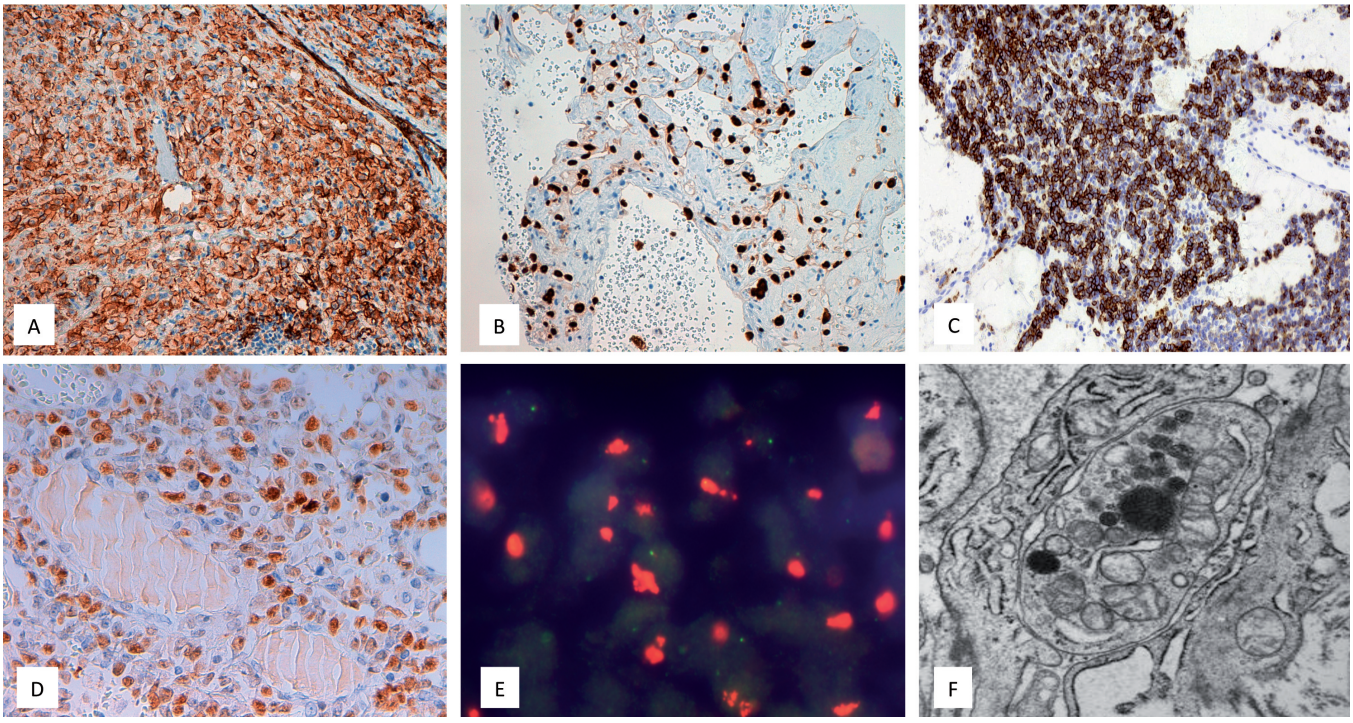

Fig. 3. Immunohistochemistry, FISH and electron microscope in AS. **A.** CD31 positivity soft tissue epithelioid AS. **B.** Nuclear ERG expression in well-differentiated cutaneous AS. **C.** D2-40 immunoreactivity in round cell AS. **D.** MYC nuclear immunoexpression in breast secondary AS. **E.** MYC amplification (FISH) in secondary AS. **F.** Electron microscopy showing Weibel-Palade bodies in AS. A-C, x 20; D, x 40.

immunoreactivity are not completely specific for AS since many other benign and malignant tumors of diverse histogenesis (carcinomas, sarcomas or lymphomas) may sometimes disclose immunoreactivity for one or various of these markers (Backer and Schnitt, 2017; Alves and Rimola, 2019; Di Battista et al., 2020). A list of source, dilution and staining pattern of vascular markers is summarized in Table 1.

Secondary AS shows consistent MYC expression by IHC (Fig. 3D), but primary AS may sporadically reveal MYC immunoreactivity (Guo et al., 2011; Fernandez et al., 2012; Mentzel et al., 2012; Shon et al., 2014; Laé et al., 2015; Udager et al., 2016; Ginter et al., 2017; Requena et al., 2017; Requena et al., 2018; Papke and Hornick, 2020). Although MYC immunoreactivity cannot discriminate between primary and secondary AS, this protein expression has not been observed in radiation-induced sarcomas other than AS (Ginter et al., 2017; Requena et al., 2017, 2018; Papke and Hornick, 2020).

Unusual expression of either or both the epithelial (EMA and cytokeratins) and neuroendocrine markers (synaptophysin, chromogranin-A) with focal or diffuse staining patterns has been reported in vascular tumors, such as AS and composite hemangioendotheliomas. This aberrant expression of unusual markers in AS increases the list of differential diagnoses, especially in cases with poorly-differentiated histology (Antonescu, 2014; Tessier Cloutier et al., 2014; Ko and Billings, 2015; Ginter et al., 2017; Wang et al., 2017a,b; Shustef et al., 2017; Machado et al., 2018; Papke and Hornick, 2020).

Electron microscopy may provide important clues in the final diagnosis of AS (Seo and Min, 2003; Carpino et al., 2005). The ultrastructural identification of Weibel-Palade bodies (Fig. 3F) confirms the occurrence of endothelial differentiation in AS.

Biology of angiosarcoma. The potential role of tumor microenvirontment

Fig. 4 depicts the main factors related to angiosarcoma biology (Tannapfel et al., 2001; Mellberg et al., 2009; Kan et al., 2012; Young et al., 2014; Liau et al., 2015; Bagaria et al., 2018; Florou and Wilky, 2018; Khan et al., 2018; Habeeeb and Rubin, 2019; Weidema et al., 2019a,b; Painter et al., 2020). All these factors are interrelated. The main genetic and epigenetic alterations are described in section 5. In this section we summarize the angiogenic factors, oncogenic pathways and tumor microenvironment factors.

Angiogenesis in AS

AS expresses multiple angiogenic growth factors, including VEGF, and both primary and secondary AS have increased expression of angiogenic tyrosine kinase receptor transcripts, including VEGFR1/2/3, implying an activated angiogenic program (Mellberg et al., 2009; Buehler et., 2013; Young et al., 2014; Khan et al., 2018; Weidema et al., 2019a,b). In addition, many AS have one or more mutations in several angiogenesis-related genes, consequently several angiogenic pathways are upregulated or mutated in a large proportion of AS.

The ANGPT-TIE system is essential to

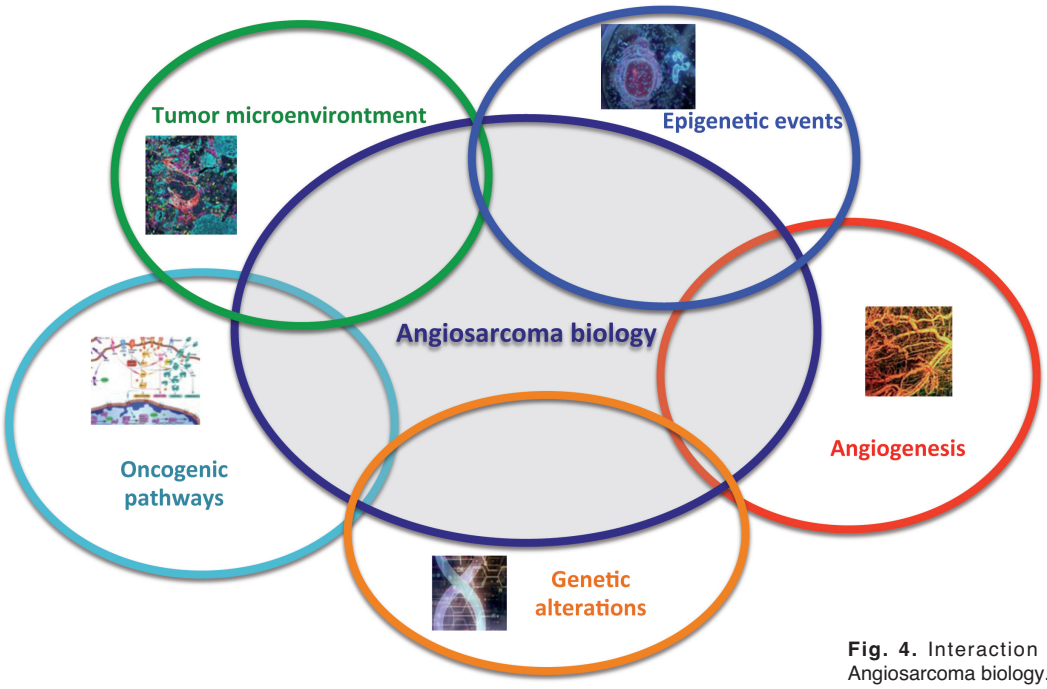

Fig. 4. Interaction effects of several factors in Angiosarcoma biology.

developmental angiogenesis and consists of two tyrosine kinase receptors, TIE1 and TEK (TIE2), and three corresponding ligands, angiopoietins-1, 2 and 4. Angiopoietin-1 and 2 play a key role in maintaining the integrity of existing vessels, vascular remodelling and angiogenesis (Mellberg et al., 2009; Buehler et al., 2013; Young et al., 2014; Khan et al., 2018). Buehler et al. reported a cohort of 56 AS where 62% of tumors expressed at least low levels of angiopoietin-2 (Buehler et al., 2013). This finding is consistent with endothelial differentiation and is related to the upregulation of Angiopoietin-2 mRNA in AS when compared with other soft tissue sarcomas (Buehler et al., 2013). The study by Buehler et al. demonstrated that increased expression of ANGPT-TIE system components was associated with both a well-differentiated histological pattern and improved overall survival. In contrast, loss of expression was associated with poor histological differentiation and more aggressive disease (Buehler et al., 2013).

Bevacizumab, Pazopanib, Sorafenib and Axitinib have been used as targeted therapy linked to angiogenesis in AS and a wide spectrum of tumor responses have been reported (Weidema et al., 2019a,b).

Oncogenic pathways in angiosarcoma

Genetic alterations involving the RAS/RAF/MEK/Erk pathway have been reported in a variable proportion of AS ranging from no mutation on *NRAS/BRAF* to mutations in 53% of AS samples (Behjati et al., 2014; Murali et al., 2015; Weidema et al., 2019a,b). An additional oncogenic pathway of interest in AS is the PI3K/AKT/mTOR-pathway, which is known to control cell survival, cell growth and cell cycle progression (Weidema et al., 2019a,b). Mutations of the PIK3CA gene have been reported in less than 20% of AS (Behjati et al., 2014; Weidema et al., 2019a,b). Finally, the p16(INK4A) pathway is also involved in AS, and genomic studies have revealed loss of CDKN2A in 26% of AS from different origins (Murali et al., 2015). Previous studies have demonstrated poor survival in patients with soft tissue sarcomas and loss of p16, but no significant difference in survival has been reported in AS patients (Weidema et al., 2019a,b).

Microenvironment in angiosarcoma

The response rate to chemo-radiotherapy in AS is usually low, therefore alternative therapeutic options are urgently needed, particularly in patients with metastatic disease (Honda et al., 2016; Shimizu et al., 2016; Sindhu et al., 2017; Botti et al., 2017; D'Angelo et al., 2018; Wollina, 2018; Florou and Wilky, 2019; Weidema et al., 2019a,b). The use of immune checkpoint inhibitors is a promising treatment modality that has yielded long-term clinical benefits in historically therapeutically refractory cancers (D'Angelo et al., 2018). The immunologic tumor microenvironment in AS has not been systematically studied, with controversial results regarding prognosis reported in limited studies (Shimizu et al., 2016; Sindhu et al., 2017; Botti et al., 2017; D'Angelo et al., 2018; Wollina, 2018; Florou et al., 2019; Weidema et al., 2019a,b). Shimizu et al. reported PD-L1 immunoreactivity related with poor prognosis in cutaneous AS (Shimizu et al., 2016), but Botti et al. in a cohort of primary AS did not confirm a prognostic significance of PD-L1 immunoexpression in AS (Botti et al., 2017). Despite the controversial results for PD-L1 expression and prognosis in AS, a complete response has been described in AS treated with CTLA-4 monotherapy (Sindhu et., al. 2017; Weidema et al., 2019a,b). This finding may in part be related to an overall mutation burden in some AS that confer a relative clinical benefit from checkpoint inhibition (Weidema et al., 2019a,b). At present, it is unclear as to what degree previous treatment altered the tumor microenvironment to subsequently sensitize them to checkpoint inhibition (Shimizu et al., 2016; Sindhu et al., 2017). Although PD-L1 expression appears to be present in a subset of AS, the relationship between PD-L1 IHC expression and susceptibility to anti-PD-1 treatment is so far unclear. These findings suggest a need for a thoughtful and targeted approach to the use of immunotherapy in AS (Weidema et al., 2019a,b). The tumor microenvironment has been postulated to limit immune cell infiltration and impair their function in the tumors (D'Angelo et al., 2018; Wollina, 2018; Florou et al., 2019; Weidema et al., 2019a,b). AS may have different tumor microenvironments depending on the location (soft tissue, breast, viscera or cutaneous). Indeed, the stromal compartment is highly heterogeneous in AS and may influence the interrelationship between stroma, neoplastic cells, and immune cells. Further studies are critical to better characterize the immune microenvironment of AS, especially the effects of location and implication of previous therapy.

Molecular biology as an emerging tool in a differential diagnosis workflow of AS and other vascular neoplasms

AS includes a genetically heterogeneous group of tumors with various molecular alterations, including gene amplifications, point mutations, translocations or gene fusions as well as epigenetic alterations (Antonescu, 2009; Guo et al., 2011; Benhjati et al., 2014; Knösel et al., 2014; Huan et al., 2016, 2017; da Costa et al., 2017; Habeed and Rubin, 2019; Beca et al., 2020; Painter et al., 2020). Table 2 summarizes the main genetic alterations and their clinical significance.

MYC plays a key oncogenic role in AS, and *MYC* gene amplification (Fig. 3E) and MYC protein overexpression have been well documented in this type of sarcoma (Manner et al., 2010; Guo et al., 2011; Fernandez et al., 2012; Ginter et al., 2014; Huang et al., 2016; Weidema et al., 2019a,b; Painter et al., 2020). *MYC* gene amplification (Fig. 3E) is almost the exclusive genetic anomaly in many secondary AS, being

present in around 55% of all secondary AS and up to 91% of secondary AS in breast (Guo et al., 2011; Fernandez et al., 2012; Ginter et al., 2014; Huang et al., 2016; Weidema et al., 2019a,b; Painter et al., 2020). Accordingly, *MYC* amplification is a useful tool to differentiate between primary and secondary AS, even in morphologically indistinguishable tumors (Fernandez et al., 2012; Ginter et al., 2014; Knösel et al., 2014; Huang et al., 2016; Habeed and Rubin, 2019; Beca et al., 2020; Painter et al., 2020). Moreover, *MYC* amplification has not been found in either PRAVP or radiation-induced sarcomas other than AS (Guo et al., 2011; Fernandez et al., 2012; Ginter et al., 2014). It is important to remark that *MYC* gene amplification is often, but not always, related to MYC protein overexpression (Fernandez et al., 2012; Ginter et al., 2014; Huang et al., 2016). Thus, MYC overexpression has been observed in 24% of primary AS without *MYC* amplification, suggesting an alternative potential regulatory pathway for MYC protein expression, such as epigenetic control in some primary AS (Fernandez et al., 2012; Ginter et al., 2014; Huang et al., 2016). Co-amplification of *FLT4* (VEGFR3) with *MYC* has been identified in 25% of secondary AS (Guo et al., 2011, Weidema et al., 2019a,b) and *KDR* mutation has been noted typically in breast AS and is apparently mutually exclusive with *PLCG1* mutation (Behjati et al., 2014; Huang et al., 2016; Weidema et al., 2019a,b, Beca et al., 2020; Painter et al., 2020).

PLCG1 (Phospholipase C, gamma 1) and *PTPRB* (Protein Tyrosine Phosphatase, Receptor Type B) are two angiogenic genes related to AS carcinogenesis (Behjati et al., 2014; Huang et al., 2016). Around 26% of AS have inactivating *PTPRB* mutations, while 9% of AS have activating *PLCG1* mutations (Huang et al., 2016; Weidema et al., 2019a,b; Painter et al., 2020). *PTPRB* alterations have been reported in 45% of secondary AS or AS with unknown primary or secondary scenario, in addition secondary AS may exhibit concomitant *MYC* amplification and *PTPRB* or *PLCG1* mutation (Behjati et al., 2014; Huang et al., 2016; Weidema et al., 2019a,b; Painter et al., 2020). Although primary AS usually lack *PTPRB* mutations, either primary or secondary AS may harbour *PLCG1* mutations (Behjati et al., 2014; Huang et al., 2016; Weidema et al., 2019a,b; Painter et al., 2020). Overall, almost all AS with *PLCG1* mutation will also harbour *PTPRB* mutations, however only half of AS with *PTPRB* mutations reveal *PLCG1* mutation (Huang et al., 2016; Weidema et al., 2019a,b).

CIC (capicua transcriptional repressor) is found in 9% of primary AS, genetic alterations include mutation, mutation and rearrangement or rearrangement without mutation. These AS subtypes with *CIC* alteration usually have round/epithelioid morphology, worse prognosis and specific clinical presentation (younger age at presentation) (Huang et al., 2016)

Corradini et al. recently reported a high mutation burden in *TP53, EGFR, KRAS, HRAS, NRAS* and *hTERT* genes in high grade (Grade 3) post-radiation AS. In addition, they detected *H-TER* mutation in both PRAVP and post-radiation AS, which opens up a new scenario in the association between PRAVP and secondary post-radiation AS (Corradini et al., 2020).

So far, it has been difficult to correlate clinical presentation with specific genetic alterations, such as mutations or gene amplifications, except for *MYC* amplification, which is present in the vast majority of secondary post-radiation AS (Fernandez et al., 2012; Ginter et al., 2014; Knösel et al., 2014; Huang et al., 2016; Habeed and Rubin, 2019; Beca et al., 2020; Painter et al., 2020). However, various studies have suggested a relationship between mutational genetic profile and AS location (Weidema et al., 2019a,b). For example, a recent study documented a higher frequency of *KDR* and *PIK3CA* mutations in primary breast AS in comparison with other AS (Beca et al., 2020). Another

Table 2. Main genetic alterations in Angiosarcomas (AS) with their clinical significance.

Type of genetic alteration	Genes involved	Clinical significance	References
Gene amplification	MYC	Secondary AS (post-radiation)	Behjati et al., 2014
	FLT4 amplification	Primary or secondary AS	Huang et al., 2016
	MYC and FLT4 (VEGFR-3) coamplification	25% of secondary AS	Weidema et al, 2019
Mutation	KDR (VEGFR-2)	Typically in primary breast AS	Huang et al., 2016
	PTPRB	Secondary AS > primary AS	Behjati et al., 2014
	PLCG1	Primary or secondary AS	Huang et al., 2016
	HTER	Post-radiation AS and PRAVP	Corradini et al., 2020
	TP53, EGFR, KRAS, HRAS, NRAS (high mutation burden)	High-grade secondary post-radiation AS	Corradini et al., 2020
	PIK3CA	High frequency in primary breast AS	Behjati et al., 2014
Translocation or gene fusion	CIC	Worse prognosis and younger age at presentation	Huang et al., 2016
	EWSR1–ATF1, CEP85L–ROS1	Sporadically described in primary AS, but not specific.	Marks et al., 2019
	NUP160-SLC43A3	Cutaneous AS	Marks et al., 2019
Epigenetic alteration	Cluster A	Post-radiation secondary AS	Weidema et al., 2019, 2020
	Cluster B	Visceral and soft tissue AS	

AS, angiosarcoma; PRAVP, post-radiation atypical vascular proliferation.

study reported *ATRX* loss to be significantly associated with deep soft tissue and hepatic AS, while decreased NOTCH1 and NOTCH2 expression were more frequent in cutaneous and visceral AS, respectively (Panse et al., 2018). Likewise, Verbeke et al. also observed that TGF-β signaling and PTEN expression differ between bone and soft tissue AS (Verbeke et al., 2013). *NUP160-SLC43A3* gene fusion has been discovered in one case of cutaneous AS (Shimozono et al., 2015) and although the detection of fusion genes, including *EWSR1–ATF1* or *CEP85L–ROS1*, has been reported in AS (Marks et al., 2019), these were seen in single cases, and were not specific to AS. The *SLC43A3* gene is associated with microvascularization which may contribute to the pathogenesis of angiosarcoma (Marks et al., 2019).

DNA methylation in AS has been poorly investigated, although Weidema et al. recently performed a methylation profiling study, where for the first time they demonstrated different AS clusters in 36 angiosarcoma samples from different locations (Weidema et al., 2019a,b, 2020). These clusters correlated well with clinical subtype, overall survival and chromosomal stability (Weidema et al., 2019a,b, 2020). Notably, UV-induced AS and post-radiation AS fell in cluster A, while both visceral and soft tissue AS almost exclusively fell into cluster B (Weidema et al., 2019a,b, 2020). This finding supports the idea that AS pathogenesis may be related to tumor location or previous external damage (radiation treatment).

Molecular methods have certainly enriched the reproducible assessment of vascular neoplasms. As a result, molecular approaches provide better and more precise diagnosis and classification, which assists in discovering potential targets for treatment.

Differential diagnosis in AS beyond tumor location and previous exposure to external carcinogenic factors.

Tumor location and previous exposure to external risk substances (radiotherapy treatment) influence the dynamic of differential diagnosis in AS. Here we review the most important differential diagnoses (Fig. 5).

Cutaneous angiosarcomas

Although Kaposi sarcoma, pseudomyogenic hemangioendothelioma (PHE) and benign cutaneous vascular proliferation/malformation may enter in the differential diagnosis of cutaneous AS, the most challenging differential diagnosis is post-radiation atypical vascular proliferation (PRAVP) (Hunt and Santa Cruz 2004; Weaver and Billings, 2009; Fisher, 2013; Ginter et al., 2014, 2017; Baker and Schnitt, 2017; Shon

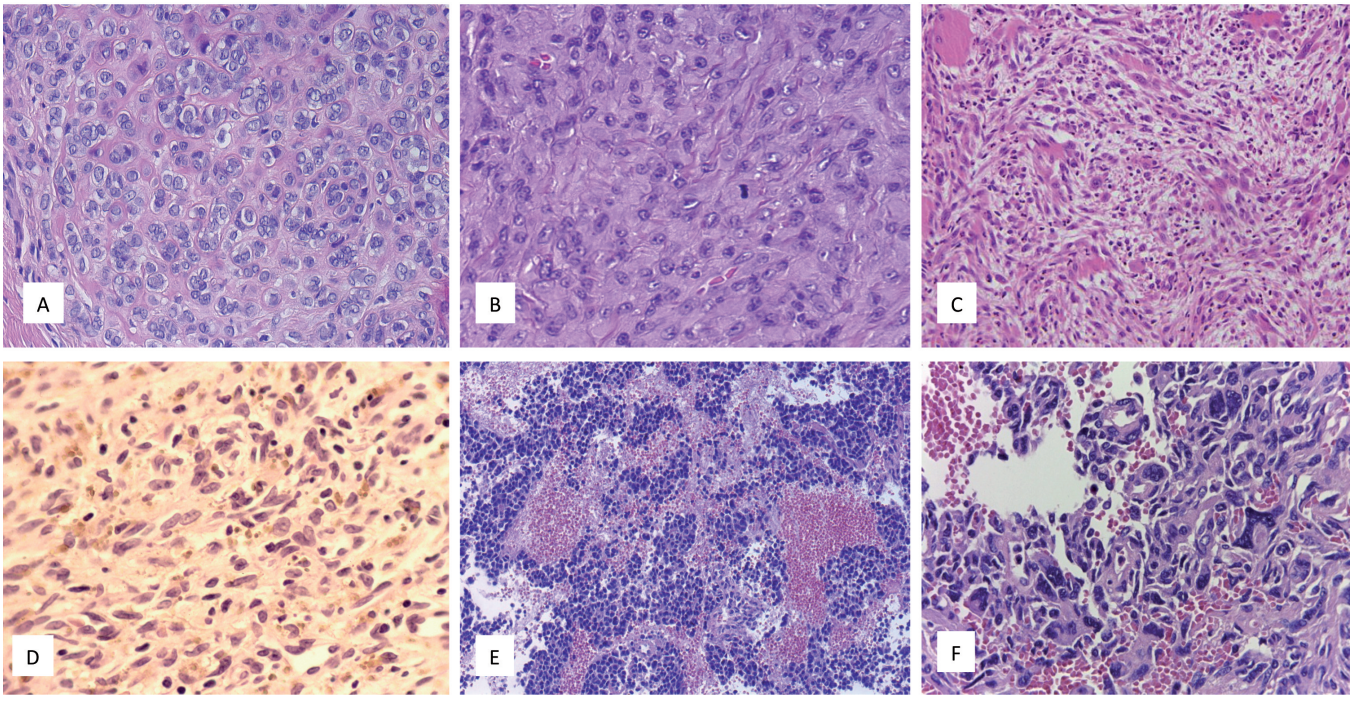

Fig. 5. Differential diagnosis in AS. **A.** Epitheliod hemangioma, H&E. **B.** Epithelioid hemangioendothelioma with mitoses, H&E. **C.** Pseudomyogenic hemangioendothelioma H&E. **D.** Kaposi sarcoma with hemosiderin deposits, H&E. **E.** Ewing sarcoma with pseudoangiomatous (hemangioendothelial) growth pattern, H&E. **F.** Pleomorphic undifferentiated sarcoma with pseudovascular pattern mimic a pleomorphic or anaplastic AS, H&E. A, B, D, F, x 40; C, E, x 20.

and Billings, 2017; Shustef et al., 2017; Weiss and Goldblum, 2019; Papke and Hornick, 2020). The differential diagnosis is even more challenging when dealing with a cutaneous lesion in a patient with a previous history of radiotherapy. In both tumors (well-differentiated AS and PRAVP) the histology shows dilated vessels with hyperchromatic endothelial cells with variable nuclear atypia and commonly lack of necrosis (Fig. 2C). Of note, PRAVP is a relatively well-circumscribed and not infiltrative lesion with anastomosing growth pattern of irregular slit-like vascular spaces dissecting dermal collagen but not extending into the subcutis (Hunt and Santa Cruz 2004; Weaver and Billings, 2009; Fisher, 2013; Ginter et al., 2014, 2017; Baker and Schnitt, 2017; Shon and Billings, 2017; Weiss and Goldblum, 2019; Papke and Hornick, 2020). In addition, PRAVP usually reveal less nuclear atypia and mitoses. In contrast, cutaneous AS display multilayering of endothelial cells, evident nuclear atypia, conspicuous nucleoli, mitoses and extension into deep dermis and subcutaneous tissues even in initial stages (Hunt and Santa Cruz 2004; Weaver and Billings, 2009; Fisher, 2013; Ginter et al., 2017; Papke and Hornick, 2020). While histological analysis may provide significant clues in the differential diagnosis when dealing with small biopsies, the IHC and molecular approach usually helps to reach an accurate diagnosis, especially in lesions with uncertain histological features. PRAVP has not been found to overexpress MYC protein or reveal *MYC* amplification so far, thus the knowledge of MYC protein and gene status can be a useful tool in differential diagnosis (Hunt and Santa Cruz 2004; Weaver and Billings, 2009; Guo et al., 2011; Fisher, 2013; Ginter et al., 2014, 2017; Baker and Schnitt, 2017; Shon and Billings, 2017; Shustef et al., 2017; Weiss and Goldblum, 2019; Papke and Hornick, 2020). Of note, MYC overexpression may be observed in a small proportion of primary cutaneous AS; thus MYC protein status by IHC does not provide additional information in the differential diagnosis between primary and secondary AS (Fernandez et al., 2012; Ginter et al., 2014; Corradini et al., 2020).

Kaposi sarcoma (KS) may resemble a well-differentiated AS but usually displays a characteristic clinical picture with histological spindle cell proliferation, hemosiderin deposits, vascular clefts and intracytoplasmic hyaline globules (Figure). This entire histological finding in addition to the nuclear HHV-8 immunoreactivity (Fig. 5D) facilitates an accurate diagnosis (Schwartz et al., 2003).

PHE most often arises in the extremities of young adult males and many cases have cutaneous involvement (Antonescu, 2014; Ko and Billings, 2015; Papke and Hornick, 2020). Under optical light microscope, the tumor is composed of plump spindle cell proliferation (Fig. 5C), neutrophilic inflammation, and scattered cells with epithelioid morphology, while some spindle cells harbour distinctive brightly eosinophilic cytoplasm with rhabdomyoblast appearance (Antonescu, 2014; Ko and Billings, 2015; Sugita et al., 2016; Shon and Billings, 2017; Hung et al., 2017; Habee and Rubin, 2019; Papke and Hornick, 2020; Ramos-Fuentes et al., 2020). Tumor cells express cytokeratin and FOSB, but are negative for S100 and desmin (Sugita et al., 2016; Shon and Billings, 2017; Hung et al., 2017; Habee and Rubin, 2019; Papke and Hornick, 2020). FOSB immunoreactivity with strong and diffuse nuclear expression is highly specific for PHE and although FOSB overexpression is not limited to PHE, this positivity, together with the histology, offers very important clues in narrowing the final diagnosis. *SERPINE1-FOSB* gene fusion is exclusive so far for PHE (Papke and Hornick, 2020).

Atypical fibroxanthoma (AFX) is a dermal spindle-histiocytoid cell tumor that typically occurs on the sun-damaged skin of head and neck in elderly people. In AFX, either prominent vascularization or extensive hemosiderin deposits may mimic AS (Mentzel et al., 2017). Adding a vascular marker to the IHC panel, such as CD31 and ERG (usually negative in AFX), helps to rule out AS (Mentzel et al., 2017). In addition, CD10 immunoreactivity favours AFX since AS does not present CD10 expression (Kaddu et al., 2002; Soleymani et al., 2019).

The differential diagnosis of cutaneous AS with benign vascular lesions (hemangiomas, lymphangiomas etc) and vascular malformation is relatively straightforward and usually does not require additional IHC or molecular analysis (Baker and Schnitt, 2017). Detailed differential diagnosis with specific benign vascular lesions with predominant cutaneous clinical presentation is beyond the scope of the present review.

Regarding malignant cutaneous lesions, poorly-differentiated squamous cell carcinoma, Merkel cell carcinoma or melanoma may occasionally present a pseudoangiomatous pattern resembling AS, hence in this setting, clinical correlation and IHC analysis is very important to define the accurate histogenesis of the tumor (Hunt and Santa Cruz, 2004; Fisher, 2013; Baker and Schnitt, 2017; Machado et al., 2018). In addition, cutaneous leiomyosarcoma (LMS) may also resemble a cutaneous AS with spindle cell morphology, positivity for at least two smooth muscle immunohistochemical markers (SMA, Desmin, H-Caldesmon) favours the diagnosis of LMS.

Breast angiosarcomas

AS represent the most common sarcoma of the breast and occur most frequently secondary to radiation therapy for breast carcinoma or secondary to longstanding lymphedema, frequently in older female patients (Baker and Schnitt, 2017; Abdou et al., 2019; Beca et al., 2020; Corradini et al., 2020). Breast AS may also arise as primary sarcoma of the breast, more commonly in younger patients (Abdou et al., 2019). Secondary AS often presents with skin changes, and primary AS presents as a palpable mass (Abdou et al., 2019). The histopathological features range from morphologically

low grade tumors demonstrating well-formed vessels with mild cytologic atypia, to histologically high-grade tumors showing pleomorphism, mitoses and a solid growth pattern resembling an undifferentiated sarcoma (Baker and Schnitt, 2017; Abdou et al., 2019; Beca et al., 2020; Corradini et al., 2020). Furthermore, cutaneous secondary AS arising in the breast area demonstrate the same morphological features as any extramammary cutaneous secondary AS (see section of cutaneous AS). The most deep-seated tumors have a morphological spectrum similar to those AS located in soft tissues (see section on soft tissue AS). PRAVP, pseudoangiomatous stromal hyperplasia (PASH), benign vascular lesions (hemangioma, angiolipoma), metaplastic carcinoma and other sarcomas with pseudoangiomatous growth patterns or extensive hemosiderin deposits are within the differential diagnostic spectrum (Ginter et al., 2014, 2017, 2019; Baker and Schnitt 2017; Abdou et al., 2019; Beca et al., 2020; Corradini et al., 2020). The morphological differential diagnostic consideration with PRAVP is described in the cutaneous AS section. *MYC* amplification is seen in secondary breast AS and not seen in PRAVP, in addition, *FLT4* co-amplification is observed in a subset of secondary AS, but not in PRAVP or other radiation-associated sarcomas (Guo et al., 2011; Fernandez et al., 2012; Mentzel et al., 2012; Beca et al., 2020). PASH represents a benign proliferation of stromal cells with an anastomosing pattern of slit-like clefts lined by a single layer of flat spindle cells simulating vascular spaces that may resemble a low-grade AS, especially in limited biopsy material (Mantilla et al., 2016; Baker and Schnitt, 2017; Ginter et al., 2017). The presence of vascular channels containing red blood cells with invasion into breast parenchyma, papillary endothelial growth and endothelial cells with hyperchromatic nuclei and mitoses in addition to vascular marker immunoreactivity favour low-grade AS. In contrast, in PASH the spindle cells display hormonal receptor positivity (oestrogen and progesterone) (Mantilla et al., 2016; Baker and Schnitt, 2017; Ginter et al., 2017). The presence of a convincing infiltrative growth pattern in AS is a major feature that will distinguish a well-differentiated AS from benign vascular lesions (hemangioma etc.) (Mantilla et al., 2016; Baker and Schnitt, 2017; Ginter et al., 2017). An angiosarcomatous component in a metaplastic breast carcinoma is a rare event, but a spindle cell component in breast metaplastic carcinoma may resemble a spindle cell AS, therefore the identification of any histological epithelial component or epithelial differentiation is important to reach a definite diagnosis (Baker and Schnitt 2017; Abdou et al., 2019; Beca et al., 2020; Corradini et al., 2020). The differential diagnosis with other sarcomas with a pseudoangiomatous growth pattern is detailed in the soft tissue tumor section. It is important to remark that a strong clinical correlation is mandatory in breast AS diagnosis, and so during the diagnostic workflow of breast tumor in patients with a previous history of radiation therapy, the possibility of post-radiation AS should be promptly excluded.

Soft tissue angiosarcomas

Differential diagnosis in soft tissue AS is related predominantly to morphological findings, either the histological pattern or cytological appearance (epithelioid, spindle, round or anaplastic tumor).

Epithelioid AS

Differential diagnosis of epithelioid AS is extensive, and includes benign and malignant lesions with mesenchymal, epithelial or melanocytic differentiation. Epithelioid hemangioma (EH) (Fig. 5A) and epithelioid hemangioendothelioma (EHE) (Fig. 5B) are vascular neoplasms that may occasionally resemble a well-differentiated epithelioid AS, although AS with epithelioid morphology usually exhibit more significant nuclear atypia and mitoses, hence further molecular analysis is not usually required (Hunt and Santa Cruz, 2004; Fisher, 2013; Antonescu, 2014; Ko and Billings, 2015; Matoso and Epstein, 2015; Shon and Billings, 2017; van IJzendoorn et al., 2017; Alves and Rimola, 2019; Habeeb and Rubin, 2019; Rosenbaum et al., 2020; Papke and Hornick, 2020). In cases with an unconvincing histological picture, intravascular growth, prominent stromal inflammation and FOS rearrangement or FOSB overexpression favour EH (Fisher, 2013; Antonescu, 2014; Habeeb and Rubin, 2019; Rosenbaum et al., 2020; Papke and Hornick, 2020). Of note, FOS rearrangement or FOSB overexpression are not specific for EH since other tumors may display these anomalies, for instance pseudomyogenic hemangioendothelioma and osteoblastoma (Habeeb and Rubin, 2019; Rosenbaum et al., 2020; Papke and Hornick, 2020). Histologically, EHE is composed of predominantly epithelioid cells embedded in myxochondroid or sclerotic hyalinized stroma and the presence of evident intracytoplasmic vacuolation (Fig. 5B) is a useful diagnostic clue (Habeeb and Rubin, 2019; Rosenbaum et al., 2020; Papke and Hornick, 2020). Nuclear pleomorphism, necrosis and increased mitotic activity are not exceptional in EHE and in such cases the differential diagnosis with epithelioid AS is more challenging.

CAMTA1 immunoreactivity or CAMTA1 (Calmodulin binding transcription activator 1) rearrangement favour a diagnosis of EHE (Habeeb and Rubin, 2019; Rosenbaum et al., 2020; Papke and Hornick, 2020), although a subcategory of EHE may reveal TFE3 immunoreactivity instead of CAMTA1 (Habeeb and Rubin, 2019; Rosenbaum et al., 2020; Papke and Hornick, 2020). Gene fusions *WWTR1-CAMTA1*, and less frequently *YAP1-TFE3*, have both been described in EHE, but not in other epithelioid mesenchymal soft tissue tumors or in a wide range of other vascular tumors/proliferations (Habeeb and Rubin, 2019; Papke and Hornick, 2020).

Carcinomas, melanomas and epithelioid malignant mesenchymal tumors, such as sclerosing epithelioid fibrosarcoma and epithelioid sarcoma are a potential

differential diagnosis of epithelioid AS and vascular markers (ERG, CD31, D2-40, VE-cadherin), MUC4, S100, SOX10 and INI1 are often necessary to resolve this differential (Hunt and Santa Cruz, 2004; Fisher, 2013; Antonescu, 2014; Ko and Billings, 2015; Matoso and Epstein, 2015; Shon and Billings, 2017; van IJzendoorn et al., 2017; Alves and Rimola, 2019; Habeeb and Rubin, 2019; Rosenbaum et al., 2020; Papke and Hornick, 2020). Epithelioid AS can express CK or EMA immunoreactivity and may be confused with metastatic carcinoma, especially in limited biopsy material. Nevertheless, unlike carcinomas, epithelioid AS almost always present intense diffuse staining for endothelial immunomarkers (Fisher, 2013; Antonescu, 2014; Habeeb and Rubin, 2019; Rosenbaum et al., 2020; Papke and Hornick, 2020).

Spindle cell AS

Spindle cell hemangioma (SCH) and composite hemangioendothelioma (CHE) are potential vascular candidates for differential diagnosis when dealing with spindle cell AS (Marusic and Billings, 2017; Habeeb and Rubin, 2019; Papke and Hornick, 2020). SCH is considered a benign neoplasm, the histology of which resembles the combination of cavernous hemangioma and KS, hence the KS area may resemble spindle cell AS. IDH1 (isocitrate dehydrogenase) or IDH2 mutations represent diagnostically significant findings in support of SCH (Habeeb and Rubin, 2019; Papke and Hornick, 2020). CHE may harbour focal areas with a low-grade angiosarcoma-like histological pattern that may be confused with spindle cell AS, but which usually have other intermixed or combined patterns including retiform hemangioendothelioma-like, spindle cell hemangioma-like or EHE-like. Endothelial marker immunoreactivity is the rule; however, neuroendocrine differentiation, possibly related to poor prognosis, has been reported (Habeeb and Rubin, 2019; Papke and Hornick, 2020). Molecular studies do not provide additional diagnostic information.

Other spindle cell sarcomas (synovial sarcoma, MPNST, fibrosarcoma, leiomyosarcoma), metastatic spindle cell/desmoplastic melanoma or sarcomatoid carcinoma are potential differential diagnoses of spindle cell AS, although the integration of clinical findings, specific IHC profile and the complement of specific molecular studies usually provide an accurate final diagnosis (Fisher, 2013; Antonescu, 2014; Habeeb and Rubin, 2019; Papke and Hornick, 2020). It is essential to emphasize that IHC findings are not completely specific in AS and pathologists should be aware that many vascular markers may be expressed in a wide variety of tumor types, many of which are included in the histological differential diagnosis of AS.

Round cells or anaplastic AS

Round cell or anaplastic AS are the less frequent variants, and the differential diagnosis should be established especially with the Ewing family of tumors (EFT), Ewing-like tumors (ELT), rhabdomyosarcomas and pleomorphic undifferentiated sarcomas, metastatic carcinomas with anaplastic morphology (predominantly lung or pancreatic carcinoma), malignant melanoma or less frequently CD30 anaplastic lymphoma (Antonescu, 2014; Machado et al., 2018; Habeeb and Rubin, 2019; Papke and Hornick, 2020). It should be noted that neuroendocrine differentiation in some AS, especially round cell AS with a solid pattern (lack of vascular formation) can complicate the differential diagnosis with neuroendocrine tumors and EFT (Machado et al., 2018). In addition, EFT may reveal a hemangioendothelial pattern (Fig. 5E) and vascular marker immunoreactivity such as FLI1 and ERG positivity (Machado et al., 2018). In this setting, additional IHC and molecular studies may help to differentiate between Ewing tumors and AS. CD31 and D2-40 expression is very rare in EFT. Furthermore, neither nuclear NKX2.2 positivity, PAX7 positivity, strong membranous CD99 immunoreactivity, nor the *EWSR1* rearrangement have been documented in AS to date (Machado et al., 2018). Conversely, the differential diagnosis between ELS with CIC-rearrangement and round cell AS may still be challenging considering that D2-40 and CD31 immunoreactivity has been reported in *CIC*-rearranged sarcomas, and *CIC* rearrangement has been reported in a subset of AS (Yoshida et al., 2016; Machado et al., 2018). Undifferentiated pleomorphic soft tissue sarcoma (UPS) and poorly-differentiated AS (Fig. 5F) are difficult to distinguish, especially in AS with poor vascular marker immunoreactivity. Furthermore, AS may result as a dedifferentiation process in other sarcomas such as MPNST, leiomyosarcoma, liposarcoma (da Cunha et al., 2005) or malignant solitary fibrous tumor, hence MDM2 or STAT6 immunoreactivity may help in this setting. Differential diagnosis with carcinoma, melanoma and anaplastic lymphoma is discussed in the visceral AS section.

Visceral angiosarcomas

Poorly-differentiated AS, especially those with solid morphology can closely mimic poorly-differentiated carcinoma, melanoma or anaplastic lymphoma (Seo and Min, 2003; Ko and Billings, 2015; Baker and Schnitt, 2017; Ginter et al., 2017; Habeeb and Rubin, 2019; Jung et al., 2019; Alves and Rimola, 2019, Papke and Hornick, 2020). In addition, AS (especially epithelioid subtype) and poorly-differentiated carcinomas may demonstrate IHC similarities (Seo and Min, 2003; Ko and Billings, 2015; Ginter et al., 2017; Habeeb and Rubin, 2019; Jung et al., 2019; Alves and Rimola, 2019, Papke and Hornick, 2020). In visceral tumors (liver, heart etc.) with clear, well-defined vasoformation, AS diagnosis is relatively straightforward, but challenging when epithelioid or spindle morphology predominates (Alves and Rimola, 2019). Notably, the fact that

epithelioid AS are positive for cytokeratin markers prompts us to consider epithelial histogenesis. Given the overlapping histological and IHC features in both, a panel of IHC stains is often needed to distinguish between carcinomas and poorly-differentiated AS arising in visceral organs (Alves and Rimola, 2019; Machado et al., 2019). ERG and CD31 are rarely expressed in carcinomas or melanomas and melanocytic marker expression (S100, SOX10, Melan A and HMB45) has not so far been found in AS (Alves and Rimola, 2019; Machado et al., 2019).

CD30 IHC expression occurs in a noteworthy subset of AS and creates a problem of differential diagnosis with other CD30-positive malignancies, especially anaplastic large cell lymphomas (ALCL), diffuse large B-cell lymphomas and germ cell tumors, some of which may be morphologically very similar to epithelioid AS (Alimchandani et al., 2014). In addition, AS may co-occur with germ cell tumors. Expression of various endothelial markers is rare in anaplastic lymphoma or germ cell tumors and lymphoid markers or germ cell immunomarkers are not expressed in AS to our knowledge (Alimchandani et al., 2014).

In conclusion, the integration of clinical, morphological, immunohistochemical and molecular findings are relevant in AS diagnosis. There is no doubt that molecular studies provide significant clues, especially in the differential diagnosis with other vascular neoplasms; nevertheless, a thorough hematoxylin and eosin analysis remains an essential tool in AS diagnosis.

Acknowledgements. This work is supported by grant GV/2019/085 from the Conselleria d'Innovació, Universitats, Ciència i Societat Digital of Generalitat Valenciana. The authors thank David Harrison for assistance with English editing.

References

Abdou Y., Elkhanany A., Attwood K., Ji W., Takabe K. and Opyrchal M. (2019). Primary and secondary breast angiosarcoma: single center report and a meta-analysis. Breast Cancer Res. Treat. 178, 523-533.

Abraham J.A., Hornicek F.J., Kaufman A.M., Harmon D.C., Springfield D.S., Raskin K.A., Mankin H.J., Kirsch D.G., Rosenberg A.E., Nielsen G.P., Desphpande V., Suit H.D., DeLaney T.F. and Yoon S.S. (2007). Treatment and outcome of 82 patients with angiosarcoma. Ann. Surg. Oncol. 14, 1953-1967.

Agaimy A., Ben-Izhak O., Lorey T., Scharpf M. and Rubin B.P. (2016). Angiosarcoma arising in association with vascular Dacron grafts and orthopedic joint prostheses: clinicopathologic, immunohistochemical, and molecular study. Ann. Diagn. Pathol. 21, 21-28.

Alimchandani M., Wang Z.F. and Miettinen M. (2014). CD30 expression in malignant vascular tumors and its diagnostic and clinical implications: a study of 146 cases. Appl. Immunohistochem. Mol. Morphol. 22, 358-362.

Alves V.A.F. and Rimola J. (2019). Malignant vascular tumors of the liver in adults. Semin Liver Dis. 39, 1-12.

Antonescu C.R. (2014). Malignant vascular tumors--an update. Mod. Pathol. 27, (Suppl 1), S30-38.

Antonescu C.R., Yoshida A., Guo T., Chang N.E., Zhang L., Agaram N.P., Qin L.X., Brennan M.F., Singer S and Maki R.G. (2009). KDR activating mutations in human angiosarcomas are sensitive to specific kinase inhibitors. Cancer Res. 69, 7175-7179.

Baker G.M. and Schnitt S.J. (2017). Vascular lesions of the breast. Semin Diagn. Pathol. 34, 410-419.

Bagaria S.P., Gatalica Z., Maney T., Serie D., Parasramka M., Attia S., Krishna M. and Joseph R.W. (2018). Association between programmed death-ligand 1 expression and the vascular endothelial growth factor pathway in angiosarcoma. Front Oncol. 8, 71.

Beca F., Krings G., Chen Y.Y., Hosfield E.M., Vohra P., Sibley R.K., Troxell M.L., West R.B., Allison K.H. and Bean G.R. (2020). Primary mammary angiosarcomas harbor frequent mutations in KDR and PIK3CA and show evidence of distinct pathogenesis. Mod. Pathol. 33, 1518-1526.

Behjati S., Tarpey P.S., Sheldon H., Martincorena I., Van Loo P., Gundem G., Wedge D.C., Ramakrishna M., Cooke S.L., Pillay N., Vollan H.K.M., Papaemmanuil E., Koss H., Bunney T.D., Hardy C., Joseph O.R., Martin S., Mudie L., Butler A., Teague J.W., Patil M., Steers G., Cao Y., Gumbs C., Ingram D., Lazar A.J., Little L., Mahadeshwar H., Protopopov A., Al Sannaa G.A., Seth S., Song X., Tang J., Zhang J., Ravi V., Torres K.E., Khatri B., Halai D., Roxanis I., Baumhoer D., Tirabosco R., Amary M.F., Boshoff C., McDermott U., Katan M., Stratton M.R., Futreal P.A., Flanagan A.M., Harris A. and Campbell P.J. (2014). Recurrent PTPRB and PLCG1 mutations in angiosarcoma. Nat. Genet. 46, 376-379.

Botti G., Scognamiglio G., Marra L., Pizzolorusso A., Di Bonito M., De Cecio R., Cantile M. and De Chiara A. (2017). Programmed death ligand 1 (PD-L1) expression in primary angiosarcoma. J. Cancer 8, 3166-3172.

Buehler D., Rush P., Hasenstein J.R., Rice S.R., Hafez G.R., Longley B.J. and Kozak K.R. (2013). Expression of angiopoietin-TIE system components in angiosarcoma. Mod. Pathol. 26, 1032-1040.

Buehler D., Rice S.R., Moody J.S., Rush P., Hafez G.R., Attia S., Longley B.J. and Kozak K.R. (2014). Angiosarcoma outcomes and prognostic factors: a 25-year single institution experience. Am. J. Clin. Oncol. 37, 473-479.

Carpino F., Pezzoli F., Petrozza V., Carpino G., Evangelista A., Mutone D., Reali M. and Gaudio C. (2005). Angiosarcoma of the heart: structural and ultrastructural study. Eur. Rev. Med. Pharmacol. Sci. 9, 231-240.

Corradini A.G., Asioli S., Morandi L., Brotto M., Righi A., Iommi M., Agostinelli C., Rucci P., Asioli S., Sapino A., Viale G. and Foschini M.P. (2020). Post-radiotherapy vascular lesions of the breast: immunohistochemical and molecular features of 74 cases with long term follow up and literature review. Histopathology (in press).

da Cunha I.W., Kowalski L.P. and Soares F.A. (2005). Dedifferentiated liposarcoma of the oral cavity with angiosarcomatous dedifferentiation. Virchows Arch. 446, 456-459.

Di Battista M., Darling M.R., Scrivener E., Stapleford R., Wehrli B. and McCord C. (2020). Histologic and immunopathologic variability in primary intraoral angiosarcoma: A case report and review of the literature. Head Neck Pathol. 14, 1139-1148.

D'Angelo S.P., Mahoney M.R., Van Tine B.A., Atkins J., Milhem M.M., Jahagirdar B.N., Antonescu C.R., Horvath E., Tap W.D. and Schwartz G.K. and Streicher H. (2018). Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401):

two open-label, non-comparative, randomised, phase 2 trials. Lancet Oncol. 19, 416-426.

da Costa A., Bonner M. and Arbiser J.L. (2017). Comprehensive profiling of H-Ras signalling in angiosarcoma endothelium. Clin. Exp. Dermatol. 42, 645-647.

Doyle L.A. (2014). Sarcoma classification: an update based on the 2013 World Health Organization classification of tumors of soft tissue and bone. Cancer 120, 1763-1774.

Fayette J., Martin E., Piperno-Neumann S., Le Cesne A., Robert C., Bonvalot S., Ranchère D., Pouillart P., Coindre J.M. and Blay J.Y. (2007). Angiosarcomas, a heterogeneous group of sarcomas with specific behavior depending on primary site: a retrospective study of 161 cases. Ann. Oncol. 18, 2030-2036.

Fernandez A.P., Sun Y., Tubbs R.R., Goldblum J.R. and Billings S.D. (2012). FISH for MYC amplification and anti-MYC immunohistochemistry: useful diagnostic tools in the assessment of secondary angiosarcoma and atypical vascular proliferations. J. Cutan. Pathol. 39, 234-242.

Fisher C. (2013). Unusual myoid, perivascular, and postradiation lesions, with emphasis on atypical vascular lesion, postradiation cutaneous angiosarcoma, myoepithelial tumors, myopericytoma, and perivascular epithelioid cell tumor. Semin. Diagn. Pathol. 30, 73-84.

Florou V. and Wilky B.A. (2018). Current and future directions for angiosarcoma therapy. Curr Treat Options Oncol. 19, 14.

Florou V., Rosenberg A.E., Wieder E., Komanduri K.V., Kolonias D., Uduman M., Castle J.C., Buell J.S., Trent J.C. and Wilky B.A. (2019). Angiosarcoma patients treated with immune checkpoint inhibitors: a case series of seven patients from a single institution. J. Immunother. Cancer 7, 213.

Fujii H., Arakawa A., Utsumi D., Sumiyoshi S., Yamamoto Y., Kitoh A., Ono M., Matsumura Y., Kato M., Konishi K., Shiga T., Sano S., Sakaguchi S., Miyagawa-Hayashino A., Takahashi K., Uezato H., Miyachi Y. and Tanioka M. (2014). $CD8^+$ tumor-infiltrating lymphocytes at primary sites as a possible prognostic factor of cutaneous angiosarcoma. Int. J. Cancer 134, 2393-2402.

Fury M.G., Antonescu C.R., Van Zee K.J., Brennan M.F. and Maki R.G. (2005). A 14-year retrospective review of angiosarcoma: clinical characteristics, prognostic factors, and treatment outcomes with surgery and chemotherapy. Cancer J. 11, 241-247.

Ginter P.S., Mosquera J.M., MacDonald T.Y., D'Alfonso T.M., Rubin M.A. and Shin S.J. (2014). Diagnostic utility of MYC amplification and anti-MYC immunohistochemistry in atypical vascular lesions, primary or radiation-induced mammary angiosarcomas, and primary angiosarcomas of other sites. Hum. Pathol. 45, 709-716.

Ginter P.S., McIntire P.J. and Shin S.J. (2017). Vascular tumours of the breast: a comprehensive review with focus on diagnostic challenges encountered in the core biopsy setting. Pathology 49, 197-214.

Ginter P.S., McIntire P.J., Irshaid L., Liu Y.F. and Shin SJ. (2019). Angiomatosis of the breast: a clinicopathological and immunophenotypical characterisation of seven cases. J. Clin. Pathol. 72, 597-602.

Gourley E., Digman G., Nicolas M. and Kaushik D. (2018). Primary renal angiosarcoma. BMJ Case Rep. 2018, brc-2017-222672.

Guo T., Zhang L., Chang N.E., Singer S., Maki R.G. and Antonescu C.R. (2011). Consistent MYC and FLT4 gene amplification in radiation-induced angiosarcoma but not in other radiation-associated atypical vascular lesions. Genes Chromosomes Cancer. 50, 25-33.

Habeeb O. and Rubin B.P. (2019). The molecular diagnostics of vascular neoplasms. Surg. Pathol. Clin. 12, 35-49.

Hoang N.T., Acevedo L.A., Mann M.J. and Tolani B. (2018). A review of soft-tissue sarcomas: translation of biological advances into treatment measures. Cancer Manag. Res. 10, 1089-1114.

Honda Y., Otsuka A., Ono S., Yamamoto Y., Seidel J.A., Morita S., Hirata M., Kataoka T.R., Takenouchi T., Fujii K., Kanekura T., Okubo Y., Takahashi K., Yanagi T., Hoshina D., Hata H., Abe R., Fujimura T., Funakoshi T., Yoshino K., Masuzawa M., Amoh Y., Tanaka R., Fujisawa Y., Honda T. and Kabashima K. (2016). Infiltration of PD-1-positive cells in combination with tumor site PD-L1 expression is a positive prognostic factor in cutaneous angiosarcoma. Oncoimmunology 6, e1253657.

Huang S.C., Zhang L., Sung Y.S., Chen C.L., Kao Y.C., Agaram N.P., Singer S., Tap W.D., D'Angelo S. and Antonescu C.R. (2016). Recurrent CIC gene abnormalities in angiosarcomas: A molecular study of 120 cases with concurrent investigation of PLCG1, KDR, MYC, and FLT4 gene alterations. Am. J. Surg. Pathol. 40, 645-655.

Hung Y.P., Fletcher C.D. and Hornick J.L. (2017). FOSB is a useful diagnostic marker for pseudomyogenic hemangioendothelioma. Am. J. Surg. Pathol. 41, 596-606.

Hunt S.J and Santa Cruz D.J. (2004). Vascular tumors of the skin: a selective review. Semin. Diagn. Pathol. 21, 166-218.

Ishida Y., Otsuka A. and Kabashima K. (2018). Cutaneous angiosarcoma: update on biology and latest treatment. Curr. Opin. Oncol. 30, 107-112.

Jung H., Kim H.N., Jang Y., Park C.K. and Ha S.Y. (2019). CAMTA-1 expression in 24 cases of hepatic epithelioid hemangioendothelioma in a single institute: Diagnostic utility for differential diagnosis from hepatic angiosarcoma. In Vivo 33, 2293-2297.

Jung H., Kim H.N., Jang Y., Park C.K., Shin S.H. and Ha S.Y. (2020). Hepatic angiosarcoma: Clinicopathologic study with an investigation of ROS1 gene Rearrangements. In Vivo 34, 1463-1467.

Kaddu S., McMenamin M.E. and Fletcher C.D. (2002). Atypical fibrous histiocytoma of the skin: clinicopathologic analysis of 59 cases with evidence of infrequent metastasis. Am. J. Surg. Pathol. 26, 35-46.

Kan C.Y., Wen V.W., Pasquier E., Jankowski K., Chang M., Richards L.A., Kavallaris M. and MacKenzie K.L. (2012). Endothelial cell dysfunction and cytoskeletal changes associated with repression of p16(INK4a) during immortalization. Oncogene 31, 4815-4827.

Khan J.A., Maki R.G. and Ravi V. (2018). Pathologic angiogenesis of malignant vascular sarcomas: Implications for treatment. J. Clin. Oncol. 36, 194-201.

Kelten Talu C., Boyaci C., Leblebici C., Hacihasanoglu E. and Bozkurt E.R. (2017). Pseudoangiomatous stromal hyperplasia in core needle biopsies of breast specimens. Int. J. Surg. Pathol. 25, 26-30.

Knösel T., Altendorf-Hofmann A., Lindner L., Issels R., Hermeking H., Schuebbe G., Gibis S., Siemens H., Kampmann E. and Kirchner T. (2014). Loss of p16(INK4a) is associated with reduced patient survival in soft tissue tumours, and indicates a senescence barrier. J. Clin. Pathol. 67, 592-598.

Ko J.S. and Billings S.D. (2015). Diagnostically challenging epithelioid vascular tumors. Surg. Pathol. Clin. 8, 331-351.

Kuhn E., Ragazzi M., Ciarrocchi A., Torricelli F., de Biase D., Zanetti E., Bisagni A., Corrado S., Uccella S., La Rosa S., Bongiovanni M., Losito S. and Piana S. (2019). Angiosarcoma and anaplastic carcinoma of the thyroid are two distinct entities: a morphologic, immunohistochemical, and genetic study. Mod. Pathol. 32, 787-798.

Laé M., Lebel A., Hamel-Viard F., Asselain B., Trassard M., Sastre X.

and Kirova Y.M. (2015). Can c-myc amplification reliably discriminate postradiation from primary angiosarcoma of the breast? Cancer Radiother. 19, 168-174.

Leduc C., Jenkins S.M., Sukov W.R., Rustin J.G. and Maleszewski J.J. (2017). Cardiac angiosarcoma: histopathologic, immunohistochemical, and cytogenetic analysis of 10 cases. Hum. Pathol. 60, 199-207.

Lee K.C., Chuang S.K., Philipone E.M. and Peters S.M. (2019). Characteristics and prognosis of primary head and neck angiosarcomas: A surveillance, epidemiology, and end results program (SEER) analysis of 1250 cases. Head Neck Pathol. 13, 378-385.

Lesluyes T., Baud J., Pérot G., Charon-Barra C., You A., Valo I., Bazille C., Mishellany F., Leroux A., Renard-Oldrini S., Terrier P., Le Cesne A., Laé M., Piperno-Neumann S., Bonvalot S., Neuville A., Collin F., Maingon P., Coindre J.M. and Chibon F. (2019). Genomic and transcriptomic comparison of post-radiation versus sporadic sarcomas. Mod. Pathol. 32, 1786-1794.

Liau J.Y., Tsai J.H., Yang C.Y., Lee J.C., Liang C.W., Hsu H.H. and Jeng Y.M. (2015). Alternative lengthening of telomeres phenotype in malignant vascular tumors is highly associated with loss of ATRX expression and is frequently observed in hepatic angiosarcomas. Hum. Pathol. 46, 1360-1366.

Lodhi H.T., Inayat F., Munir A. and Ilyas G. (2018). Primary renal angiosarcoma: a diagnostic and therapeutic challenge. BMJ Case Rep. 2018, bcr-2018-225484.

Machado I., Santonja C., Huerta V., Cruz J., Requena C., Requena L. and Llombart-Bosch A. (2018). Unusual neuroendocrine differentiation in a small round cell angiosarcoma: A potential histologic mimicker of superficial ewing sarcoma. Am. J. Dermatopathol. 40, 671-675.

Manner J., Radlwimmer B., Hohenberger P., Mössinger K., Küffer S., Sauer C., Belharazem D., Zettl A., Coindre J.M., Hallermann C., Hartmann J.T., Katenkamp D., Katenkamp K., Schöffski P., Sciot R., Wozniak A., Lichter P., Marx A. and Ströbel P. (2010). MYC high level gene amplification is a distinctive feature of angiosarcomas after irradiation or chronic lymphedema. Am. J. Pathol. 176, 34-39.

Mantilla J.G., Koenigsberg T., Reig B., Shapiro N., Villanueva-Siles E. and Fineberg S. (2016). Core biopsy of vascular neoplasms of the breast: Pathologic features, imaging, and clinical findings. Am. J. Surg. Pathol. 40, 1424-1434.

Mark R.J., Poen J.C., Tran L.M., Fu Y.S. and Juillard G.F. (1996). Angiosarcoma. A report of 67 patients and a review of the literature. Cancer 77, 2400-2406.

Marks E.I., Pamarthy S., Dizon D., Birnbaum A., Yakirevich E., Safran H. and Carneiro B.A. (2019). ROS1-GOPC/FIG: a novel gene fusion in hepatic angiosarcoma. Oncotarget 10, 245-251.

Marušić Z. and Billings S.D. (2017). Histopathology of spindle cell vascular tumors. Surg. Pathol. Clin. 10, 345-366.

Matoso A. and Epstein J.I. (2015). Epithelioid angiosarcoma of the bladder: A series of 9 cases. Am. J. Surg. Pathol. 39, 1377-1382.

Matsuoka S., Koyama T., Takeda T., Yamada K., Hyogotani A., Hamanaka K., Sekiguchi N. and Koizumi T. (2019). Development of angiosarcoma in a mediastinal non-seminomatous germ cell tumor that exhibited growing teratoma syndrome during chemotherapy. Thorac. Cancer 10, 111-115.

Mellberg S., Dimberg A., Bahram F., Hayashi M., Rennel E., Ameur A., Westholm J.O., Larsson E., Lindahl P., Cross M.J. and Claesson-Welsh L. (2009). Transcriptional profiling reveals a critical role for tyrosine phosphatase VE-PTP in regulation of VEGFR2 activity and endothelial cell morphogenesis. FASEB J. 23, 1490-502.

Mentzel T., Schildhaus H.U., Palmedo G., Büttner R. and Kutzner H. (2012). Postradiation cutaneous angiosarcoma after treatment of breast carcinoma is characterized by MYC amplification in contrast to atypical vascular lesions after radiotherapy and control cases: clinicopathological, immunohistochemical and molecular analysis of 66 cases. Mod. Pathol. 25, 75-85.

Mentzel T., Requena L. and Brenn T. (2017). Atypical fibroxanthoma revisited. Surg. Pathol. Clin. 10, 319-335.

Murali R., Chandramohan R., Möller I., Scholz S.L., Berger M., Huberman K., Viale A., Pirun M., Socci N.D., Bouvier N., Bauer S., Artl M., Schilling B., Schimming T., Sucker A., Schwindenhammer B., Grabellus F., Speicher M.R., Schaller J., Hillen U., Schadendorf D., Mentzel T., Cheng DT., Wiesner T. and Griewank K.G. (2015). Targeted massively parallel sequencing of angiosarcomas reveals frequent activation of the mitogen activated protein kinase pathway. Oncotarget 6, 36041-36052.

Naka N., Ohsawa M., Tomita Y., Kanno H., Uchida A. and Aozasa K. (1995). Angiosarcoma in Japan: a review of 99 cases. Cancer 75, 989-996.

Painter C.A., Jain E, Tomson B.N., Dunphy M., Stoddard R.E., Thomas B.S., Damon A.L., Shah S., Kim D., Gómez Tejeda Zañudo J., Hornick J.L., Chen Y.L., Merriam P., Raut C.P., Demetri G.D., Van Tine B.A., Lander E.S., Golub T.R. and Wagle N. (2020). The Angiosarcoma Project: enabling genomic and clinical discoveries in a rare cancer through patient-partnered research. Nat. Med. 26, 181-187.

Panse G., Chrisinger J.S., Leung C.H., Ingram D.R., Khan S., Wani K., Lin H., Lazar A.J. and Wang W.L. (2018). Clinicopathological analysis of ATRX, DAXX and NOTCH receptor expression in angiosarcomas. Histopathology 72, 239-247.

Papke D.J. and Hornick J.L. (2020). What is new in endothelial neoplasia? Virchows Arch. 476, 17-28.

Pasquier E., André N., Street J., Chougule A., Rekhi B., Ghosh J., Philip D.S.J., Meurer M., MacKenzie K.L., Kavallaris M. and Banavali SD. (2016). Effective management of advanced angiosarcoma by the synergistic combination of propranolol and vinblastine-based metronomic chemotherapy: A bench to bedside study. E. Bio. Med. 6, 87-95.

Pawlik T.M., Paulino A.F., McGinn C.J., Baker L.H., Cohen D.S., Morris J.S., Rees R. and Sondak V.K. (2013). Cutaneous angiosarcoma of the scalp: a multidisciplinary approach. Cancer 98, 1716-1726.

Pazhenkottil A.P. and Bode P.K. (2020). Angiosarcoma Involving the Heart. N. Engl. J. Med. 382, 855.

Ramos-Fuentes H., Ortiz-Diaz C., Sifuentes-Cervantes S. and Castro-Núñez J. (2020). Pseudomyogenic hemangioendothelioma: A rare vascular tumor of the oral cavity. J. Craniofac. Surg. 31, e333-e334.

Requena C., Sendra E., Llombart B., Sanmartín O., Guillén C., Lavernia J., Traves V. and Cruz J. (2017). Cutaneous angiosarcoma: Clinical and pathology study of 16 cases. Actas Dermosifiliogr. 108, 457-465.

Requena C., Rubio L., Lavernia J., Machado I., Llombart B., Sanmartín O., Traves V., Guillén C. and Cruz J. (2018). Immunohistochemical and fluorescence in situ hybridization analysis of MYC in a series of 17 cutaneous angiosarcomas: A single-center Study. Am. J. Dermatopathol. 40, 349-354.

Rosenbaum E., Jadeja B., Xu B., Zhang L., Agaram N.P., Travis W., Singer S., Tap W.D. and Antonescu C.R. (2020). Prognostic

stratification of clinical and molecular epithelioid hemangioendothelioma subsets. Mod. Pathol. 33, 591-602.

Schwartz E.J., Dorfman R.F. and Kohler S. (2003). Human herpesvirus-8 latent nuclear antigen-1 expression in endemic Kaposi sarcoma: an immunohistochemical study of 16 cases. Am. J. Surg. Pathol. 27, 1546-1550.

Seo I.S. and Min K.W. (2003). Postirradiation epithelioid angiosarcoma of the breast: a case report with immunohistochemical and electron microscopic study. Ultrastruct. Pathol. 27, 197-203.

Sindhu S., Gimber L.H., Cranmer L., McBride A. and Kraft A.S (2017). Angiosarcoma treated successfully with anti-PD-1 therapy - a case report. J. Immunother. Cancer 5, 58.

Shon W. and Billings S.D. (2017). Cutaneous malignant vascular neoplasms. Clin. Lab. Med. 37, 633-646.

Shon W., Sukov W.R., Jenkins S.M. and Folpe A.L. (2014). MYC amplification and overexpression in primary cutaneous angiosarcoma: a fluorescence in-situ hybridization and immunohistochemical study. Mod. Pathol. 27, 509-515.

Singh R., Chufal K.S., Pahuja A.K., Suresh T., Chowdhary R.L. and Ahmad I. (2019). Primary angiosarcoma of the breast: a radiation oncologist's perspective with a concise review of the literature. BMJ Case Rep. 18, 12.

Shimozono N., Jinnin M., Masuzawa M., Masuzawa M., Wang Z., Hirano A., Tomizawa Y., Etoh-Kira T., Kajihara I., Harada M., Fukushima S. and Ihn H. (2015). NUP160-SLC43A3 is a novel recurrent fusion oncogene in angiosarcoma. Cancer Res. 75, 4458-4465.

Shimizu A., Kaira K., Okubo Y., Utsumi D., Yasuda M., Asao T,. Nishiyama M., Takahashi K. and Ishikawa O. (2016). Positive PD-L1 expression predicts worse outcome in cutaneous angiosarcoma. J. Glob. Oncol. 3, 360-369.

Shustef E., Kazlouskaya V., Prieto V.G., Ivan D. and Aung P.P. (2017). Cutaneous angiosarcoma: a current update. J. Clin. Pathol. 70, 917-925.

Sindhu S., Gimber L.H., Cranmer L., McBride A. and Kraft A.S. (2017). Angiosarcoma treated successfully with anti-PD-1 therapy - a case report. J. Immunother. Cancer 5, 58.

Soleymani T., Aasi S.Z., Novoa R. and Hollmig S.T. (2019). Atypical fibroxanthoma and pleomorphic dermal sarcoma: Updates on classification and management. Dermatol. Clin. 37, 253-259.

Subramaniam M.M., Salleh N.L., Wu B., Rozario M.A., Lim H., Puhaindran M.E., Soong R. and Lee VK. (2018). Primary epithelioid angiosarcoma of finger masquerading as epithelioid hemangioma: Report of a case and analysis of mutational pattern in epithelioid hemangiomas and angiosarcomas by next-generation sequencing. Appl. Immunohistochem. Mol. Morphol. 26, e7-e13.

Sugita S., Hirano H., Kikuchi N., Kubo T., Asanuma H., Aoyama T., Emori M. and Hasegawa T. (2016). Diagnostic utility of FOSB immunohistochemistry in pseudomyogenic hemangioendothelioma and its histological mimics. Diagn. Pathol. 11, 75.

Taffurelli M., Pellegrini A., Meattini I,. Orzalesi L., Tinterri C., Roncella M., Terribile D., Caruso F., Tazzioli G., Pollini G., Friedman D., Mariotti C., Cianchetti E., Cabula C., Thomas R., Cedolini C., Rovera F., Grassi M., Lucani G., Cappella A., Bortul M., Stacul G., Scarabeo F., Procaccini E. and Galimberti V. (2019). Secondary breast angiosarcoma: A multicentre retrospective survey by the national Italian association of Breast Surgeons (ANISC). Breast 45, 56-60.

Tannapfel A., Weihrauch M., Benicke M., Uhlmann D., Hauss J., Wrbitzky R. and Wittekind C. (2001). p16INK4A-alterations in primary angiosarcoma of the liver. J. Hepatol. 35, 62-67.

Tessier Cloutier B., Costa F.D., Tazelaar H.D. and Folpe A.L. (2014). Aberrant expression of neuroendocrine markers in angiosarcoma: a potential diagnostic pitfall. Hum. Pathol. 45, 1618-1624.

Udager A.M., Ishikawa M.K., Lucas D.R., McHugh J.B. and Patel RM. (2016). MYC immunohistochemistry in angiosarcoma and atypical vascular lesions: practical considerations based on a single institutional experience. Pathology 48, 697-704.

van IJzendoorn D.G.P. and Bovée J.V.M.G. (2017). Vascular tumors of bone: The evolvement of a classification based on molecular developments. Surg. Pathol. Clin. 10, 621-635.

Verbeke S.L., Bertoni F., Bacchini P., Oosting J., Sciot R., Krenács T. and Bovée J.V. (2013). Active TGF-β signaling and decreased expression of PTEN separates angiosarcoma of bone from its soft tissue counterpart. Mod. Pathol. 26, 1211-1221.

Wang L., Lao I.W., Yu L., Yang W. and Wang J. (2017a). Primary breast angiosarcoma: A retrospective study of 36 cases from a single chinese medical institute with clinicopathologic and radiologic correlations. Breast J. 23, 282-291.

Wang Z.B., An X.J., Deng J.F., Liu J.H. and Shi H.Y. (2017b). Characteristics of ERG, Fli-1, CD34, CD31 and FVIIIRAg expression in hepatic malignant vascular tumors. Zhonghua Bing Li Xue Za Zhi. 46, 760-763. (In chinese).

Weaver J. and Billings S.D. (2009). Postradiation cutaneous vascular tumors of the breast: a review. Semin. Diagn. Pathol. 26, 141-149.

Weidema M.E., Versleijen-Jonkers Y.M.H., Flucke U.E., Desar I.M.E. and van der Graaf W.T.A. (2019a). Targeting angiosarcomas of the soft tissues: A challenging effort in a heterogeneous and rare disease. Crit. Rev. Oncol. Hematol. 138, 120-131.

Weidema M.E., Flucke U.E., van der Graaf W.T.A., Ho V.K.Y., Hillebrandt-Roeffen M.H.S., Versleijen-Jonkers Y.M.H., Husson O. and Desar I.M.E. (2019b). Prognostic factors in a large nationwide cohort of histologically confirmed primary and secondary angiosarcomas. Cancers (Basel). 11, 1780.

Weidema M.E., van de Geer E., Koelsche C., Desar I.M.E., Kemmeren P., Hillebrandt-Roeffen M.H.S., Ho V.K.Y., van der Graaf W.T.A., Versleijen-Jonkers Y.M.H., von Deimling A. and Flucke U.E; PALGA Group. (2020). DNA Methylation Profiling Identifies Distinct Clusters in Angiosarcomas. Clin Cancer Res. 26, 93-100.

Weiss S.W. and Goldblum J.R. (2019). Enzinger & Weiss's soft tissue tumors, 6th edn: Mosby.

Wick M.R. (2016). Contributions of Dr. Juan Rosai to the pathology of cutaneous vascular proliferations: A review of selected lesions. Semin Diagn. Pathol. 33, 284-293.

Wilson G.C., Lluis N., Nalesnik M.A., Nassar A., Serrano T., Ramos E., Torbenson M., Asbun H.J. and Geller D.A. (2019). Hepatic angiosarcoma: A multi-institutional, international experience with 44 cases. Ann. Surg. Oncol. 26, 576-582.

Wollina U. (2018). Angiosarcoma: an immunogenic tumour. Br. J. Dermatol. 179, 257-258.

Yasir S. and Torbenson M.S. (2019). Angiosarcoma of the liver: Clinicopathologic features and morphologic patterns. Am. J. Surg. Pathol. 43, 581-590.

Yoshida A., Goto K., Kodaira M., Kobayashi E., Kawamoto H., Mori T., Yoshimoto S., Endo O., Kodama N., Kushima R., Hiraoka N., Motoi T. and Kawai A. (2016). CIC-rearranged sarcomas: A study of 20 cases and comparisons with ewing sarcomas. Am. J. Surg. Pathol.

40, 313-323.

Young R.J., Brown N.J., Reed M.W., Hughes D. and Woll P.J. (2010). Angiosarcoma. Lancet Oncol. 11, 983-991.

Young R.J., Fernando M., Hughes D., Brown N.J. and Woll P.J. (2014). Angiogenic growth factor expression in benign and malignant vascular tumours. Exp. Mol. Pathol. 97, 148-153.

Zeng D., Cheng J., Gong Z., Chen J., Long H. and Zhu B. (2020). A pooled analysis of primary hepatic angiosarcoma. Jpn. J. Clin. Oncol. 50, 556-567.

Zhang C., Xu G., Liu Z., Xu Y., Lin F., Baklaushev V.P., Chekhonin V.P., Peltzer K., Mao M., Wang X., Wang G. and Zhang C. (2019). Epidemiology, tumor characteristics and survival in patients with angiosarcoma in the United States: a population-based study of 4537 cases. Jpn. J. Clin. Oncol. 49, 1092-1099.

Accepted September 4, 2020