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Review

Atypical spindle cell/pleomorphic lipomatous tumor

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Summary. Atypical spindle cell/pleomorphic lipomatous tumor (ASPLT) is a recently described morphologically low-grade and clinically indolent adipocytic tumor, which will be incorporated as a new tumor entity in the upcoming 5th edition of the WHO Classification of Soft tissue and Bone tumors. Histologically, ASPLTs are characterized by ill-defined tumor margins and the presence of variable proportions of mild-to-moderately atypical spindle cells, adipocytes, lipoblasts, pleomorphic multinucleated cells and a myxoid or collagenous extracellular matrix. ASPLTs can show a wide variety of microscopic appearances and there is histologic overlap with diverse mimics. The diagnosis of ASPLT can therefore be challenging. Molecular studies have shown a consistent absence of *MDM2* or *CDK4* amplification. On the other hand, deletions or losses of 13q14, including *RB1*, have been identified in a significant subset of cases. This review provides an overview of the currently known clinical and pathological features of ASPLTs, detailing its most relevant differential diagnoses.

Key words: Atypical spindle cell/pleomorphic lipomatous tumor, Atypical spindle cell lipomatous tumor, Atypical pleomorphic lipomatous tumor, RB1, MDM2, Liposarcoma, Spindle cell/pleomorphic lipoma

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Introduction

'Atypical spindle cell/pleomorphic lipomatous tumor' (ASPLT) is a novel entity in the group of adipocytic tumors. ASPLT originated by the merging of 'atypical spindle cell lipomatous tumor' (ASLT) and 'atypical pleomorphic lipomatous tumor' (APLT).

The history of ASPLT starts in 1994, when Dei Tos et al. described a series of 6 atypical spindle cell lipomatous neoplasms, originally named 'spindle cell liposarcoma' (Dei Tos et al., 1994). 'Spindle cell liposarcomas' were then regarded as a variant of atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLS) (McCarthy and Chetty, 2018; Creytens, 2019a). In the following years, more cases of atypical spindle cell lipomatous neoplasms were reported. Aside from 'spindle cell liposarcoma', these neoplasms were also referred to as 'well-differentiated spindle cell liposarcoma', 'fibrosarcoma-like lipomatous neoplasm' and 'atypical spindle cell lipoma' (Mentzel et al., 2010; Deyrup et al., 2013; Creytens et al., 2014). In the 2002 and 2013 World Health Organization (WHO) Classification of Soft tissue and Bone tumors, 'spindle cell liposarcoma' was still considered as a spindle cell variant of ALT/WDLS (Dei Tos and Pedeutour, 2013). From there on, large scale studies, as well as the advancements in cytogenetics and molecular genetics, have led to better diagnostic criteria, the identification of characteristic molecular alterations and the development of useful ancillary diagnostic tests (Creytens et al., 2017, 2019a; Marino-Enriquez et al., 2017; McCarthy and Chetty, 2018). Clinical, histological and molecular differences between some of the atypical spindle cell lipomatous neoplasms and ALT/WDLS became clear, and it appeared that a particular subset of them did not

seem to fit into any of the existing diagnostic categories of adipocytic tumors (Creytens et al., 2019a). A separate entity therefore seemed justified. In 2017, Marino-Enriquez et al. described the clinicopathological, immunohistochemical, and molecular characteristics of this non-categorized family of low-grade adipocytic tumors with spindle cell features, for which the term ASLT was proposed (Marino-Enriquez et al., 2017). Also in 2017, Creytens et al. identified a group of low-grade pleomorphic adipocytic neoplasms with a pleomorphic lipoma-like appearance but with atypical morphologic features, for which they proposed the term APLT (Creytens et al., 2017). In their large series of cases, Creytens et al. demonstrated significant overlapping morphologic and genetic features between APLT and ASLT, suggesting that both tumors belong to a same morphologic spectrum, named ASPLT. This new entity will be incorporated in the upcoming 5th edition of the WHO Classification of Soft tissue and Bone tumors.

This review provides an overview of the currently known morphological, immunohistochemical and molecular characteristics of ASPLTs. The differential diagnoses are discussed extensively, highlighting the immunohistochemical and cytogenetic workup that is essential for accurate diagnosis.

Clinical features

Although ASPLTs can affect patients of any age, they occur mainly in middle-aged adults, with a peak incidence in the sixth decade of life (Creytens, 2019). There is a slight male predominance. The tumor appears as a persistent or enlarging soft tissue nodule or swelling. It arises in the subcutaneous fat and to a lesser extent in deep (subfascial) somatic soft tissues (Marino-Enriquez et al., 2017; Creytens et al., 2017; Bahadir et al., 2018; McCarthy and Chetty, 2018). Intradermal, intracavitary or visceral locations are exceptionally rare (Marino-Enriquez et al., 2017; Creytens et al., 2017; Bahadir et al., 2018; McCarthy and Chetty, 2018; Boyd, 2019). The anatomic distribution is wide, however, there is a predilection for the limbs and limb girdles, of which the most common locations are the hands, feet, and thighs, followed by the shoulders, buttocks, forearms, knees, lower legs and upper arms (Marino-Enriquez et al., 2017; Creytens et al., 2017; Bahadir et al., 2018; McCarthy and Chetty, 2018). Less common sites include the head and neck, genital area, trunk and back. The larynx, mediastinum, retroperitoneum, trachea and appendix are rarely affected (Marino-Enriquez et al., 2017).

Pathological features

On gross examination, ASPLTs are nodular or multinodular lesions that are (at least partly) not encapsulated (Fig. 1). The lesions often have ill-defined tumor margins and they can grow infiltratively in surrounding tissue. The tumor size varies, ranging from 0,5 cm to 28 cm and with a median size from 5 to 8,5 cm (Creytens et al., 2017; Marino-Enriquez et al., 2017; Bahadir et al., 2018).

The (variable) constituents in ASPLTs are atypical spindle cells, adipocytes, lipoblasts, pleomorphic (multinucleated) cells and extracellular matrix (Creytens et al., 2017, 2019a; Marino-Enriquez et al., 2017; Bahadir et al., 2018). The neoplastic spindle cells are elongated cells with pale eosinophilic cytoplasm, ovoid nuclei with generally smooth nuclear contours and variable hyperchromasia. The spindle cells usually have only focal and/or mild cytonuclear atypia. However, more prominent and/or diffuse atypia has been described (Creytens et al., 2017; McCarthy and Chetty, 2018). The adipocytic component consists of mature-appearing adipocytes, often with slight variation in shape and size (McCarthy and Chetty, 2018). Patchy and mild-to-moderate atypia of adipocytes, with denser chromatin, nuclear enlargement and focal bi- or multinucleation (i.e. morphological features also described in the literature as 'anisometric cell lipoma' or 'dysplastic lipoma') can be observed (Michal et al., 2018; Creytens et al., 2019a). Lipoblasts are present in almost half of cases, but usually in small numbers. Lipoblasts morphologically range

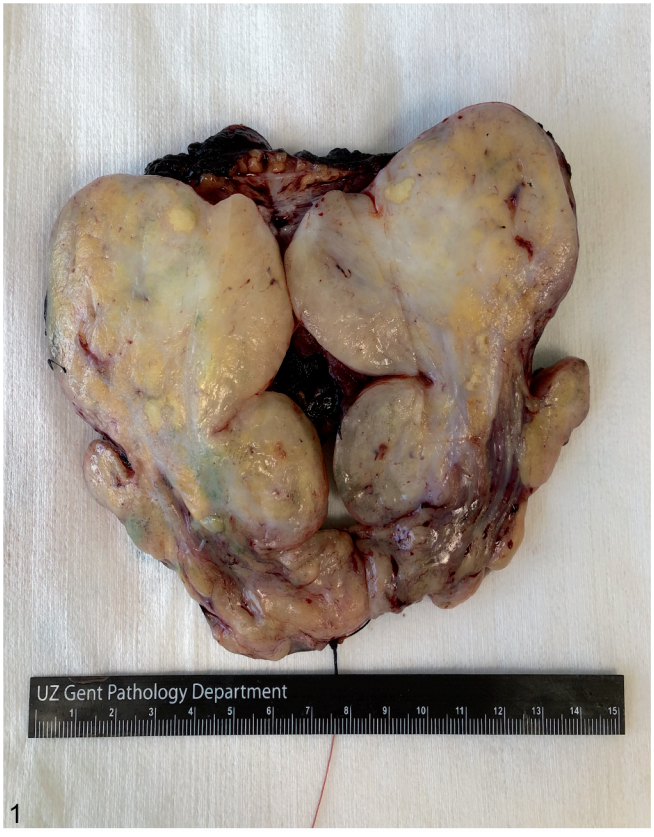


Fig. 1. Cut surface of a multinodular lesion with heterogenous fibrous and fatty aspect.

from small uni- or bivacuolated cells to larger multivacuolated cells. They have hyperchromatic, scalloped nuclei with punched out vacuoles. Bizarre, hyperchromatic, and sometimes pleomorphic multinucleated cells, are often scattered within the spindle cell or adipocytic components (Fig. 2). The extracellular matrix varies from purely myxoid to predominantly collagenous. Areas with a spindle cell/pleomorphic lipoma-like appearance composed of spindle cells intermingled with floret-like giant cells set in a fibrous to collagenous stroma are described (Fig. 3) (Creytens et al., 2017). However, the presence of bundles of ropey collagen is rather uncommon in ASPLTs (Creytens et al., 2017; Marino-Enriquez et al., 2017; McCarthy and Chetty, 2018).

ASPLTs can show a wide range of microscopic appearances, even with heterogeneous areas within the same lesion (Creytens et al., 2017, 2019a,b; Marino-Enriquez et al., 2017; McCarthy and Chetty, 2018). The microscopic appearance depends on varying cellularity, on the extremely variable proportions of the atypical spindle cells, adipocytes, lipoblasts and pleomorphic (multinucleated) cells, and on the variable aspect of the extracellular matrix. The morphology of these tumors can best be described as a broad spectrum defined by two morphological extremes, namely spindle cell-poor and spindle cell-rich variants of ASPLT (Creytens et al., 2017; McCarthy and Chetty, 2018). The spindle cell-poor extreme shows a prominent extracellular (usually) myxoid matrix with only few spindle cells and scattered mature adipocytes (also described as 'atypical spindle cell lipoma' morphology) (Fig. 4) (Creytens et al., 2014; Marino-Enriquez et al., 2017). A 'fat-rich' variant of ASPLT is another spindle cell-poor example (Fig. 5) (Creytens et al., 2019b). It is almost exclusively composed of an adipocytic component with atypical morphological features, such as variation in adipocytic size and shape as well as patchy mild-to-moderate adipocytic atypia. The diagnostic morphological features, such as cytonuclear atypia of the spindle cell component, can be very focal and subtle in the 'spindle cell-poor' variants of ASPLT and can therefore be easily missed microscopically or as a result of insufficient sampling of large lesions (McCarthy and Chetty, 2018; Creytens et al., 2019a). At the high-cellularity end of the spectrum, ASPLTs may be significantly more cellular. They are composed of numerous spindle cells showing diffuse, mild-to-moderate cytonuclear atypia, with easily identifiable lipoblasts and less extracellular matrix (also described as 'fibrosarcoma-like lipomatous neoplasm' morphology) (Fig. 6) (Deyrup et al., 2013; Marino-Enriquez et al., 2017). Mitotic figures are usually scarce (ranging from 1 to 2 mitoses per 50 high-power fields) in all ASPLT variants (Marino-Enriquez et al., 2017; Creytens et al., 2017; Bahadir et al., 2018). Tumor necrosis is always absent (Creytens et al., 2017; Bahadir et al., 2018). A rare finding is heterologous (metaplastic) differentiation, with presence of smooth muscle, cartilaginous, and/or osseous elements (Marino-Enriquez et al., 2017; Creytens et al., 2019c).

Immunohistochemical features

The neoplastic spindle cells and/or adipocytes show variable expression for CD34, S100 and desmin. The majority of cases (50-70%) show loss of nuclear Rb expression (Fig. 7). Weak and/or focal expression of MDM2 or CDK4 can be seen, but the combination of MDM2 and CDK4 expression is not compatible with the diagnosis of ASPLT (Creytens et al., 2017, 2019a; Marino-Enriquez et al., 2017; McCarthy and Chetty, 2018).

Molecular features

Molecular studies, including fluorescence in situ hybridization (FISH) and multiplex ligation-dependent probe amplification (MLPA), have shown in a significant subset of cases deletions/losses in 13q14, including deletions of tumor suppressor gene *RB1* and its adjacent genes *RCTBTB2, DLEU1* and *ITM2B*. Also, a consistent absence of *MDM2/CDK4* gene amplification was shown (Creytens et al., 2014, 2017, 2019a). In addition, monosomy for chromosome 7 has been reported in some cases (Italiano et al., 2008).

Treatment and prognosis

ASPLT is a clinically indolent adipocytic lesion. Most patients have an excellent prognosis if the lesion is completely excised. Incompletely removed lesions show local recurrence in 10 to 15% of patients. Unlike 'classical' atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLS) and dedifferentiated liposarcoma (DDLS), the risk for dedifferentiation and/or metastasis is minimal to non-existent in ASPLTs. This highlights the importance of distinguishing ASPLT from ALT/WDLS and DDLS, in order to avoid aggressive surgical resection (Creytens et al., 2017, 2019a; Marino-Enriquez et al., 2017; McCarthy and Chetty, 2018; Bahadir et al., 2018).

Differential diagnosis

ASPLTs can show a wide variety of microscopic appearances, and therefore the morphological differential diagnostic range is also broad, including benign as well as malignant soft tissue lesions (Creytens, 2020). In our view, the following differential diagnoses are the most important, ranked according to the morphological resemblance with spindle cell-poor to spindle cell-rich variants of ASPLT (Table 1).

Spindle cell/pleomorphic lipoma (SL/PL)

SL/PLs and ASPLTs both affect middle-aged adults, with a male predilection. SL/PLs are typically located in the subcutaneous fat of the posterior neck, shoulder and back (Miettinen and Mandahl, 2013). In contrast, ASPLTs have a wider anatomic distribution. The average

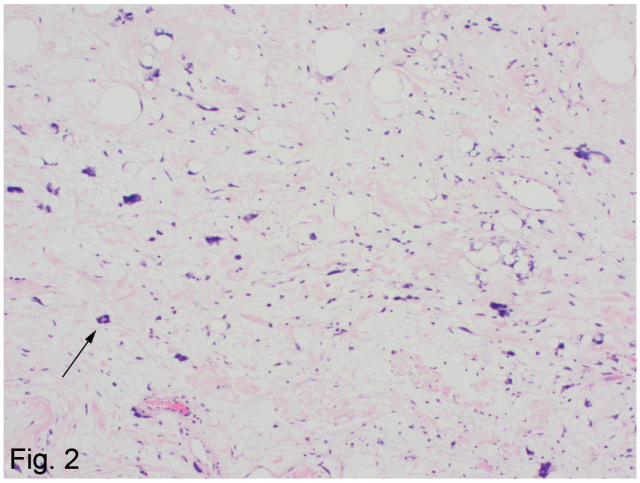
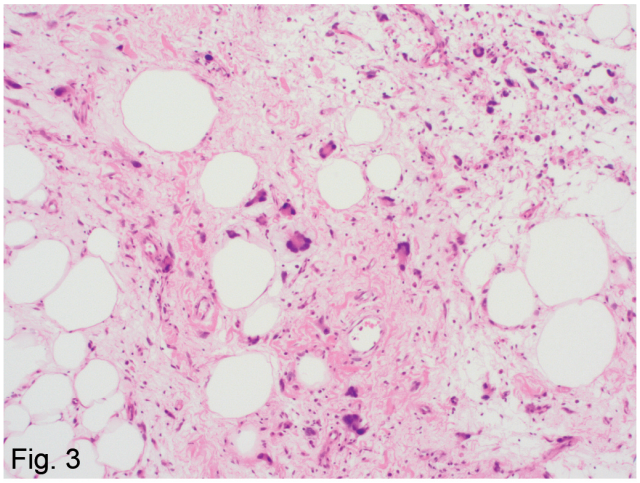


Fig. 2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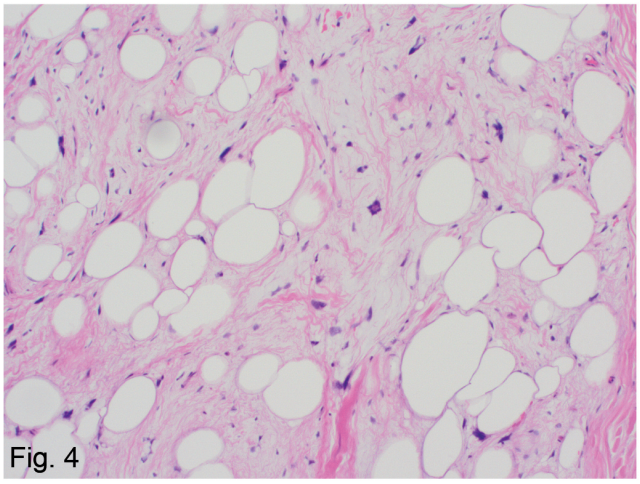
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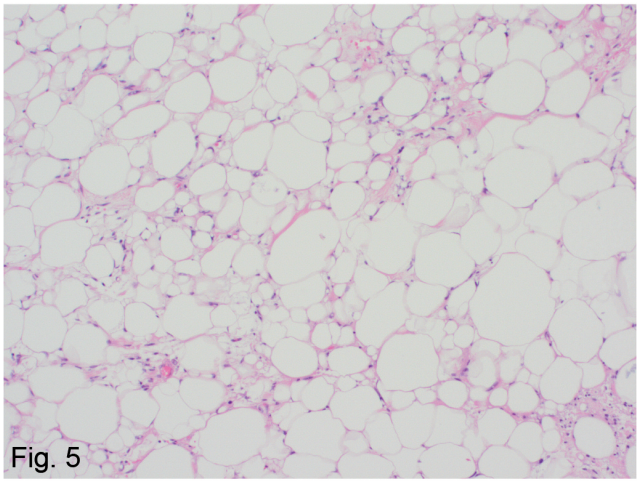
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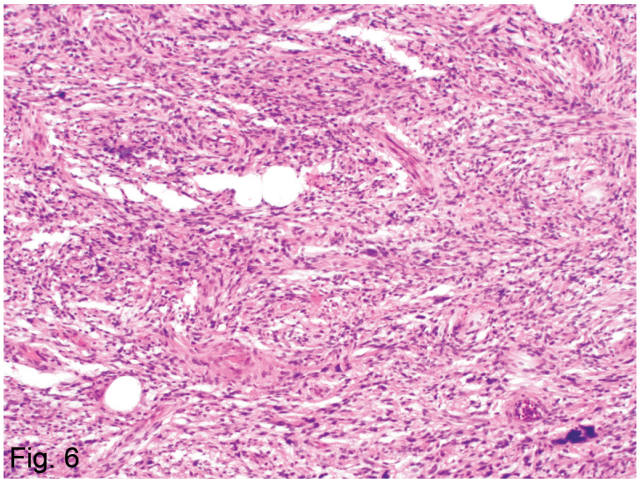
Fig. 6

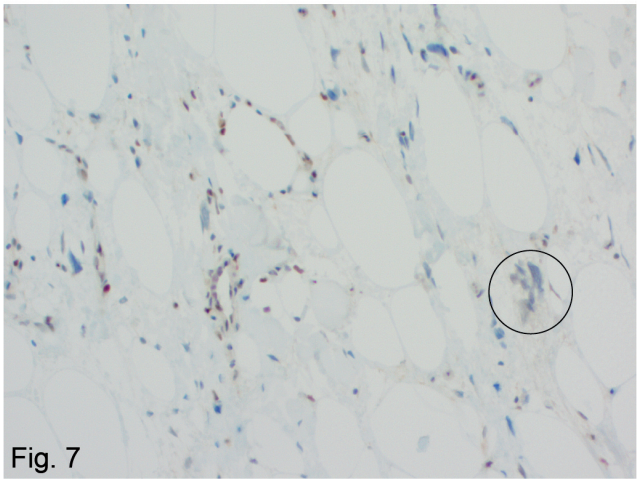
Fig. 7

Fig. 2. ASPLT, with atypical spindle cells, bizarre pleomorphic multinucleated cells, a floret-like giant cell, irregularly admixed with adipocytes and uni/bi/multivacuolated pleomorphic lipoblasts on a background of collagenous to myxoid matrix (HE). x 100.
Fig. 3. ASPLT, with mildly atypical spindle cells (with hyperchromatic nuclei), adipocytes with variation in size/shape in a collagenous background. There are bizarre pleomorphic multinucleated cells and floret-like giant cells (= 'spindle cell/ pleomorphic lipoma-like' morphology) (HE). x 100.
Fig. 4. A spindle cell-poor variant of ASPLT, with mildly atypical spindle cells (with hyperchromatic nuclei) admixed with adipocytes with variation in size/shape and set in a myxoid background. There is a floret-like giant cell and ropey-like collagen (= 'atypical spindle cell lipoma-like' morphology) (HE). x 100.
Fig. 5. A spindle cell-poor variant of ASPLT, almost exclusively composed of adipocytes with prominent variation in size/shape and mild atypia (= 'fat-rich' variant of ASPLT, mimicking a 'classical' atypical lipomatous tumor) (HE). x 100.
Fig. 6. A spindle cell-rich variant of ASPLT (= 'fibrosarcoma-like lipomatous neoplasm' morphology) (HE). x 100.
Fig. 7. Loss of Rb expression in the atypical cells, whereas lymphocytes and endothelial cells show intact Rb expression. x 200.

size of SL/PLs (4 to 5 cm) is slightly smaller than that of ASPLTs (Chen et al., 2012; McCarthy and Chetty, 2018; Van Treeck and Fritchie, 2019). Unlike ASPLTs, SL/PLs are usually well circumscribed, they are often encapsulated and they do not show infiltrative growth (Van Treeck and Fritchie, 2019). However, rare intramuscular or dermal located SL/PLs can grow more infiltratively. Recurrences are rarely seen in SL/PLs, whereas ASPLTs have a 10 to 15% recurrence rate.

Comparable with ASPLTs, SL/PLs are composed of mature adipocytes and spindle cells, frequently set in a myxoid matrix. Floret-like multinucleated cells are typical for SL/PLs. However, they can also occur in ASPLTs. As with ASPLTs, the proportion of adipocytes and spindle cells can also vary significantly in SL/PL. Some fat-poor SL/PL variants contain few or no adipocytes (McCarthy and Chetty, 2018; Van Treeck and Fritchie, 2019). The myxoid matrix of SL/PL can be abundant, resembling spindle cell-poor variants of ASPLT. In spite of all the resemblances, SL/PLs morphologically differ from ASPLTs because they do not contain atypical spindle cells or 'bizarre' pleomorphic cells, nor do they have 'atypical' multivacuolated lipoblasts (Creytens et al., 2014, 2017, 2018a,b). Furthermore, the presence of thick and eosinophilic, ropey-like collagen is almost a characteristic feature of SL/PLs, while it is rather uncommon in ASPLTs. Mitoses are very rare in SL/PL and diagnosis of a classical SL/PL should always be made with caution when (atypical) mitotic activity is present (Creytens et al., 2018a,b).

There is an immunohistochemical and molecular resemblance between SL/PLs and ASPLTs, namely the deletion of *RB1*, corresponding with immunohisto-

Table 1. Differential diagnosis of atypical spindle cell/pleomorphic lipomatous tumor.

		ASPLT	SL/PL	ALT/WDLS	DDLS	PLS	MTMF	CAF	SFT
Clinical	age (peak)	6th decade	5th to 6th decade	4th to 6th decade	5th to 6th decade	7th decade	5th to 6th decade	5th decade (F) 7th decade (M)	5th to 7th decade
	deep/ superficial	superficial > deep	superficial >> deep	deep > superficial	deep >> superficial	deep	superficial	superficial	deep
	predilection site	limbs, limb girdles	neck, shoulder, back	(lower) extremities, RP	RP, extremities, paratesticular	limbs (+ trunk, RP)	inguinal/groin area, trunk, extremities	inguinal/groin area	extremities, RP (+ head/ neck, trunk)
	size (mean or median)	5 to 8,5 cm	3 to 5 cm	> 10 cm	> 10 cm	8 to 10 cm	6,6 cm	2,8 cm (F) 7 cm (M)	5 to 10 cm
Histology	ill-defined margins	yes	no	yes	yes	yes	no	no	no
	atypical spindle cells	yes	no	possible	yes	variable	no	no	no
	lipoblasts	common	rare	possible (not required)	yes	yes (pleomorphic)	no	no	no
	pleomorphic MN cells	yes	no	possible	possible	yes	no	no	no
	mitoses	often	no	possible	variable	high	no	variable	variable
	necrosis	no	no	no	possible	common	no	no	no
	other characteristics		MN floret cells + ropey like collagen					prominent thick-walled vessels	patternless growth and branching vessels
Immunohisto-chemistry	MDM2 and CDK4 positivity	no	no	yes	yes	no	no	no	no
	Rb loss	yes (50-70%)	yes	no	no	yes	yes	yes	no
	others						desmin+ (diffuse, 90%) CD34+ (diffuse, 90%)	ER+ (over 90%) PR+ (over 90%)	STAT6+
Molecular features	*MDM2* or *CDK4* amplification	no	no	yes (close to 100%)	yes (close to 100%)	no	no	no	no
	RB1 deletion	yes	yes	no	no	yes	yes	yes	no
	others					complex karyotype non pathognomic			*NAB2-STAT6* fusion

ASPLT, atypical spindle cell/pleomorphic lipomatous tumor; SL/PL, spindle cell/pleomorphic lipoma; ALT/WDLS, atypical lipomatous tumor/well differentiated liposarcoma; DDLS, dedifferentiated liposarcoma; PLS, pleomorphic liposarcoma; MTMF, mammary-type myofibroblastoma; CAF, cellular angiofibroma; SFT, solitary fibrous tumor; ST, soft tissue; RP, retroperitoneum; ER, estrogen receptor; PR, progesterone receptor; M, male; F, female; MN, multinucleated; >, more often; >> clearly more often.

chemical nuclear loss of expression for Rb (Mentzel et al., 2010; Chen et al., 2012; Creytens et al., 2014, 2017; McCarthy and Chetty, 2018). Both entities lack amplification of the *MDM2* and *CDK4* genes, corresponding with negative immunohistochemical staining for MDM2 and CDK4 in the spindle cells and adipocytes (McCarthy and Chetty, 2018). The spindle cells of both SL/PLs and ASPLTs often show positivity for CD34 (Creytens et al., 2014, 2017; McCarthy and Chetty, 2018).

Atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLS)

ALT/WDLSs affect adults within the same age range as ASPLTs. Also similar to ASPLTs is their broad anatomic distribution, with a predilection for the extremities. Other common sites of ALT/WDLSs are the retroperitoneum, paratesticular area and mediastinum. The lesions range from very small to very large in size. Grossly, they are well circumscribed lesions, although they can have irregular borders and infiltrative growth, similar to ASPLTs. ALT/WDLSs have no metastatic potential, but dedifferentiation to a dedifferentiated liposarcoma (DDLS) occurs in up to 10% of ALT/WDLs. The risk of dedifferentiation is significantly higher in the retroperitoneum than elsewhere. Even without dedifferentiation, ALT/WDLSs are associated with significant mortality due to frequent local recurrences. The recurrence rate depends on anatomic localization and on whether or not a complete resection was achieved. There is a 15% recurrence for lesions in subcutis and 30 to 50% recurrence when in deep soft tissues of extremities or in somatic soft tissues of the trunk (Dei Tos and Pedeutour, 2013; McCarthy and Chetty, 2018; Thway, 2019).

ALT/WDLSs may be morphologically indistinguishable from a fat-rich (spindle cell-poor) variant of ASPLT, since ALT/WDLSs are almost exclusively composed of an adipocytic component with atypical morphological features, such as significant variation in adipocytic size and shape, and (at least focal) mild-to-moderate adipocytic atypia. ALT/WDLSs generally contain also atypical nonlipogenic stromal cells situated in fibrous septa, as well as a variable number of lipoblasts, varying from many to none. Lipoblasts are not required for diagnosis of ALT/WDLSs. Compared to ASPLTs, pleomorphic lipoblasts are rather rare in ALT/WDLSs (Dei Tos and Pedeutour, 2013; Creytens et al., 2017; McCarthy and Chetty, 2018).

Unlike ASPLTs, ALT/WDLSs (and also DDLSs) are characterized by supernumerary ring chromosomes or giant marker chromosomes with amplification of 12q12-15 regions (Dei Tos and Pedeutour, 2013; Thway, 2019). These aberrant chromosomes contain amplified sequences of *MDM2* and *CDK4* genes, detectable with array comparative genomic hybridization (aCGH), FISH or MLPA techniques (Creytens et al., 2015). This is reflected in immunohistochemical MDM2 and CDK4 nuclear overexpression, whereas there is no overexpression for these markers in ASPLTs (Marino-Enriquez et al., 2017; Creytens et al., 2017; Bahadir et al., 2018). Another molecular/immunohistochemical means to differentiate between ALT/WDLSs and ASPLTs is the absence of *RB1* deletion and the preserved Rb expression in ALT/WDLSs (Creytens et al., 2017, 2019a,b; Bahadir et al., 2018; McCarthy and Chetty, 2018).

Dedifferentiated liposarcoma (DDLS)

DDLSs affect middle-aged adults and elderly patients. They have a broad anatomic distribution, with the retroperitoneum as the most common site. Other regular sites are the extremities, paratesticular region and more rarely the trunk (including mediastinum and thorax) and head and neck region. The lesions are typically larger than ASPLT lesions. Grossly, DDLSs are multinodular and they typically surround adjacent visceral structures. The prognosis for DDLSs is clearly worse than for ASPLTs. Despite radical surgical excision (and often also radiotherapy), DDLSs have a local recurrence rate of approximately 40%. Unlike ASPLTs and ALT/WDLSs, DDLSs have a metastatic potential with metastasis in up to 30% of cases. Mortality is often due to uncontrollable local recurrences (Dei Tos et al., 2013; McCarthy and Chetty, 2018; Thway, 2019).

DDLSs have a variety of morphological appearances. The majority of DDLS are highly cellular and non-lipogenic, composed of moderate-to-marked atypical spindle cells arranged in loose fascicles, and with a storiform or patternless architecture. The mitotic index is variable, and necrosis can be seen (Dei Tos et al., 2013; McCarthy and Chetty, 2018; Thway, 2019). A minority of DDLSs are morphologically 'low-grade', with sparsely-to-moderately cellular fibroblast-like spindle cell proliferations with mild nuclear atypia and scant mitotic figures (Dei Tos et al., 2013; Thway, 2019). 'Low-grade' DDLSs may be morphologically indistinguishable from ASPLTs on the spindle cell-rich end of the spectrum. Clues to identify DDLSs are the presence of an abrupt transition from a well-differentiated adipocytic component into non-lipogenic spindle cell areas, as well as the presence of higher-grade areas, widespread atypia or cellular pleomorphism (Marino-Enriquez et al., 2017; McCarthy and Chetty, 2018). Compared to ASPLTs, pleomorphic lipoblasts are extremely rare in DDLSs, but they have been reported in very rare DDLSs with 'homologous' lipoblastic (pleomorphic liposarcoma-like) differentiation (Marino-Enriquez et al., 2010; Dei Tos et al., 2013).

DDLSs are characterized by the same aberrations in chromosome 12 as ALT/WDLSs, with copy number gains of *MDM2* and *CDK4* genes (Dei Tos et al., 2013; Thway, 2019). DDLSs can be distinguished from ASPLTs by MDM2 and CDK4 immunohistochemistry or by aCGH, FISH or MLPA testing for *MDM2* and/or

CDK4 gene amplification (Creytens et al., 2017, 2019a,b; Thway, 2019).

Pleomorphic liposarcoma (PLS)

PLSs affect middle aged and elderly patients. Unlike ASPLTs, PLSs have a deep (subfascial) location and are only rarely localized in subcutaneous fat (Coindre and Pedeutour, 2013; Anderson and Jo, 2019). The anatomic distribution is similar to ASPLTs, with limbs as most occurring site, and trunk and retroperitoneum as less common locations. The average size of PLSs is typically larger than of ASPLTs. PLSs are well-demarcated, though not encapsulated and they often show infiltrative growth. PLSs have a significant metastatic potential and they have an overall mortality rate of about 50% (Coindre and Pedeutour, 2013; Anderson and Jo, 2019).

Morphologically, PLSs contain a varying proportion of pleomorphic lipoblasts in a background of a high-grade, usually pleomorphic, undifferentiated sarcoma. The presence of pleomorphic lipoblasts is necessary for the diagnosis, but their number varies between cases and between areas within the same tumor (Coindre and Pedeutour, 2013; Anderson and Jo, 2019). PLSs can be differentiated from ASPLTs by a higher degree of pleomorphism, high mitotic activity and tumor necrosis (Creytens et al., 2017). In addition, the presence of a PL-like component demonstrating floret-like giant cells is not present in PLSs (Creytens et al., 2017).

PLSs may show nuclear loss of expression for Rb, also corresponding with loss of RB1 and its flanking genes, as seen with ASPLTs (Creytens et al., 2017). However, the genetic alterations are more complex than in ASPLTs, with more losses and gains and with multiple structural rearrangements (Creytens et al., 2017; Anderson and Jo, 2019). The genetic aberrations in PLSs are not consistent and not specific; there are no pathognomonic structural rearrangements, such as a recurrent translocation or a consistent presence of supernumerary ring chromosomes (Coindre and Pedeutour, 2013; Creytens et al., 2019a).

Mammary-type myofibroblastoma (MTMF)

MTMF is a benign mesenchymal lesion, first described in the breast. It is now known to have a wide anatomical distribution. MTMFs most commonly occur in the groin, inguinal area, trunk and lower extremities. They are well circumscribed lesions with a median size of 5,5 cm. They occur mostly in middle-aged men. These clinical characteristics of MTMFs are more or less the same as of ASPLTs (McMenamin and Debiec-Rychter, 2013; Howitt and Fletcher, 2016).

MTMFs share morphological features with ASPLTs. MTMFs are spindle cell proliferations with a variably prominent lipomatous component and the stroma is typically collagenous, and occasionally hyalinized or myxoid (McMenamin and Debiec-Rychter, 2013; Howitt and Fletcher, 2016). Tumor cellularity may vary from markedly cellular to paucicellular and hyalinized. In contrast to ASPLTs, the spindle cells in MTMFs generally show no atypia, the adipocytes show only minimal variation in size and shape and there are no lipoblasts (Marino-Enriquez et al., 2017; Bahadir et al., 2018).

Immunohistochemically, unlike ASPLTs, MTMFs are typically diffuse positive for desmin and CD34 (in 90% of cases) (McCarthy and Chetty, 2018; Bahadir et al., 2018). Only rare cases are negative for both markers. Expression of SMA is present in one third of cases. MTMFs show the same 13q14 deletions as ASPLTs, with deletion of *RB1* gene and corresponding nuclear loss of expression for Rb (McMenamin and Debiec-Rychter, 2013; Howitt and Fletcher, 2016; McCarthy and Chetty, 2018).

Cellular angiofibroma (CAF)

CAF is a benign fibroblastic mesenchymal tumor. Females and males are more or less equally affected. In contrast with ASPLTs, CAFs are generally limited to genital or inguinal regions. Extragenital locations, such as the retroperitoneum, pelvic and lumbar region, urethra, trunk and oral mucosa, are rare. CAFs are typically well circumscribed (Flucke et al., 2011; Fletcher et al., 2013a).

CAFs are cellular fibroblastic lesions composed of bland spindle-shaped (sometimes epithelioid) cells in a patternless pattern. Up to 50% of CAFs also contain a limited adipocytic component (of usually 5% or less) (Flucke et al., 2011; Fletcher et al., 2013a). In contrast with ASPLTs, there are numerous small-to-medium sized thick-walled blood vessels, often with perivascular fibrosis or hyalinization. These vessels may also contain fibrin thrombi. The stroma in CAFs can be myxoid, with wispy (rather than ropey) collagen (McCarthy and Chetty, 2018). Lesions in female patients may have brisk mitotic activity. There are no atypical mitotic figures and there is no necrosis (Flucke et al., 2011; Fletcher et al., 2013a; McCarthy and Chetty, 2018).

Similar to ASPLTs, CAFs are usually positive for CD34 (up to 60%) and loss of nuclear Rb staining is also a characteristic finding in both (Flucke et al., 2011; Creytens et al., 2017). Genetically, CAFs also show deletions in the 13q14 region, with deletion of *RB1*. Variable expression of SMA and desmin is described in a minority of cases. CAFs show expression for progesterone receptor (PR) and estrogen receptor (ER) (in over 90% of cases) (Flucke et al., 2011; Fletcher et al., 2013a; McCarthy and Chetty, 2018).

Fat-forming solitary fibrous tumor (SFT)

Fat-forming SFT is a recognized rare morphological variant of SFT. Fat-forming SFTs usually affect middle-aged adults. They mostly occur in deep soft tissues of the lower extremities and retroperitoneum. Other sites include the orbits, pleura, perineum, spine and mediastinum (Lee and Fletcher, 2011; Fletcher et al.,

2013b). Most fat-forming SFTs have an indolent clinical course. However, the biological behavior of (all) SFTs is unpredictable. Tumors demonstrating a combination of high mitotic activity (≥4/10 HPF), increased cellularity, atypia, tumor necrosis and infiltrative growth have traditionally been termed 'malignant' SFTs, but new risk stratification models predict prognosis more accurately (Fletcher et al., 2013b; Demicco et al., 2017).

Fat-forming SFTs are morphologically similar to conventional SFTs, except for the presence of a variably prominent adipocytic component. They are composed of bland spindle cells with a patternless architecture embedded in a variably collagenized stroma and admixed with a variable number of mature adipocytes. In contrast with ASPLTs, SFTs typically contain many branching 'staghorn-like' blood vessels. However, the presence of staghorn-like vessels in a collagenous-rich background (reminiscent of SFTs) is described as a rare peculiar growth pattern in ASPLTs (Creytens et al., 2017, 2019a,b). There are usually no lipoblasts in SFTs and the spindle cells and adipocytes show no cytonuclear atypia (except for the histologically malignant SFTs) (Fletcher et al., 2013b).

Virtually all SFTs (including the fat-forming variants) show nuclear STAT6 expression, due to the *NAB2-STAT6* fusion gene (Chmielecki et al., 2013; Marino-Enriquez et al., 2017; McCarthy and Chetty, 2018). STAT6 is a sensitive and specific marker for SFTs (Doyle et al., 2014). ASPLTs show no STAT6 immunopositivity (Creytens et al., 2017). Besides positivity for STAT6, almost all SFTs demonstrate immunohistochemical nuclear expression for CD34, CD99 and Bcl2 (McCarthy and Chetty, 2018). Unlike ASPLTs, SFTs are not characterized by deletion of *RB1* gene and corresponding nuclear loss of expression for Rb (Creytens et al., 2017; McCarthy and Chetty, 2018).

Diffuse neurofibroma (with entrapment of fat)

Diffuse neurofibromas are often located within the dermis and subcutaneous fat of young patients, which is a clearly different clinical setting compared with ASPLTs. They are ill-defined with diffuse and infiltrative spread through subcutaneous tissues. The most common site of diffuse neurofibromas is the head and neck region. Although diffuse neurofibromas are considered benign lesions, recurrence may occur even if completely excised. Malignant transformation is rare (Marino-Enriquez et al., 2017; McCarthy and Chetty, 2018).

Diffuse neurofibromas are composed of a monomorphic proliferation of spindle cells with waved nuclei (Marino-Enriquez et al., 2017). Adipocytic differentiation is rare, but entrapment of adjacent fat may occur (Marino-Enriquez et al., 2017; McCarthy and Chetty, 2018). This is how diffuse neurofibromas can simulate a spindle cell lesion with an adipocytic component. Degenerative atypia with localized hyperchromatic atypical cells is possible. The detection of hyperplastic nerve bundles and Meissnerian corpuscles can aid in the identification of diffuse neurofibromas (Antonescu et al., 2013; McCarthy and Chetty, 2018; Marino-Enriquez et al., 2017).

Diffuse neurofibromas show S100, SOX10 and ('fingerprints-like') CD34 positivity (Marino-Enriquez et al., 2017; McCarthy and Chetty, 2018). In contrast with ASPLTs, there is a preserved Rb expression and absence of *RB1* deletion.

Conclusions

Since the publication of the 2013 WHO Classification of Soft tissue and Bone tumors, there have been substantial steps forward in the clinicopathologic and molecular (cyto)genetic characterization of a heterogeneous group of 'atypical low-grade adipocytic neoplasms with spindle cell features', for which the term atypical spindle cell/pleomorphic lipomatous tumor (ASPLT) has been proposed. The diagnosis of ASPLT can be challenging and the morphological differential diagnostic range can be broad in view of the wide variety of microscopic appearances of these adipocytic tumors. Recognition of morphologic clues, as well as judicious application of immunohistochemical and molecular ancillary techniques to confirm the diagnosis and exclude mimics, are crucial. This review highlights the clinicopathological and molecular features, as well as the most important differential diagnoses of this novel tumor entity, which will be incorporated in the upcoming 5th edition of the WHO Classification of Soft tissue and Bone tumors.

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