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Review Article

A Practical and Comprehensive Immunohistochemical Approach to the Diagnosis of Superficial Soft Tissue Tumors

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Abstract: Soft tissue tumors include neoplasms of specific and unknown lineages, and, therefore, lineage markers of smooth muscle, skeletal muscle, endothelial, epithelial and Schwann cells have proven useful in everyday practice. However, groups of tumors remain that are defined essentially on grounds of histology; others can be defined by molecular genetic studies. The complex distribution patterns of many antigens and loss of some differentiation antigens in malignant tumors often necessitate the use of panels of antibodies. Optimally such panels should address all significant differential diagnostic alternatives. There is little doubt that numerous new differentiation markers will appear in the future. The evaluation of tumor proliferation, apoptosis, and cell cycle control will give new information related to tumor biology and prognosis.
Key Words: Soft tissue tumors, skin, immunohistochemistry

Introduction

Immunohistochemistry (IHC) is presently the most important adjunct tool in the evaluation of soft tissue tumors because of its practicability and relatively low cost [1]. As more data has accumulated over the years, typical diagnostic patterns for many tumor types have emerged. Nevertheless, many diagnoses, such as those of fibrous, fibro-histiocytic and lipomatous tumors, are still based on histology. Furthermore, a small group of soft tissue tumors remains unclassified despite extensive ancillary studies. Because of the complex patterns of expression of many antigens, the use of panels of antibodies is often necessary. New modalities of antigen recovery, especially heat induced antigen/epitope retrieval, have made possible the application of many antibodies that previously were believed reactive only in frozen tissues. Standardization of reagents, optimization of techniques, and proactive quality assurance are vitally important for the success of diagnostic IHC [2]. This review summarizes the application of the most important IHC tools as applied to the diagnosis of specific types of superficial soft tissue tumors. Earlier reviews discussed the biology of specific antigens, such as intermediate filament proteins, S100 protein, muscle cell, and neural antigens [3-5]. Other ancillary tests, such as molecular genetic tests for translocation-specific fusion transcripts, are becoming useful in the evaluation of such specific tumor types as myxoid liposarcoma, alveolar rhabdomyosarcoma, synovial sarcoma, clear cell sarcoma, Ewing's sarcoma, and desmoplastic small round cell tumor [6].

Fibroblastic/Myofibroblastic Tumors

There are no universally applicable markers for fibroblastic lineage. However, similar to subsets of dermal and soft tissue fibroblasts, some fibroblastic neoplasms, such as dermatofibrosarcoma protuberans (DFSP) and solitary fibrous tumors are positive for CD34, the haematopoietic progenitor cell antigen also expressed in endothelial cells [7-10]. In contrast, other fibroblastic tumors including benign fibrous histiocytoma (FH), desmoid and nodular fasciitis are generally negative for CD34, although occasional benign FHs (5-

10%) have been CD34-positive [7, 11]. DFSPs that have undergone fibrosarcomatous transformation commonly lose the CD34 expression [2, 13]. Benign FH typically shows a significant factor XIIIa-positive cell population, whereas DFSP is negative [7, 14]. Another potentially useful marker in the differential diagnosis of FH, cellular FH and DFSP is CD163 as it was reported to be positive in most FHs and cellular FHs with DFSPs being mostly negative [15]. In addition, CD44 has been claimed to be positive in dermatofibroma rather than DFSP [16]. These preliminary data is still to be validated. A panel composed of CD34, factor XIIIa, CD163 and CD44 will have a significantly higher sensitivity and specificity in this differential diagnosis. However, if any histologic doubts exist, FISH techniques will give the answer [17].

Fibromatoses are locally aggressive myofibroblastic proliferations that are characterised by higher rate of recurrence. Higher levels of nuclear β-catenin have been reported in all types of fibromatoses (superficial and deep) [18, 19]. However, a subset of other soft tissue lesions such as solitary fibrous tumor, low grade myofibroblastic sarcoma and synovial sarcoma may show B-catenin immunoreactivity [20, 21].

Fibroblastic/myofibroblastic sarcoma is a controversial group of low grade sarcomas with a prominent myofibroblastic differentiation [22]. The immunophenotype of these lesions is variable but they are consistently positive for at least one myogenic marker 23]. In one study, all cases of myofibroblastic sarcoma were positive for smooth muscle actin (SMA) and 2/3 of cases were positive for calponin, whereas none reacted with either smooth muscle myosin (SMMS) or h-caldesmon. This reaction pattern was similar to that seen in nodular fasciitis and fibromatosis [24].

The haemosiderotic fibrolipomatous tumor is histologically characterised by the presence of mature adipose tissue and spindle cell component accompanied by haemosidern pigment deposition within macrophages, in the cytoplasm of some of the spindle cells and also within the extracellular stroma. The spindle cell component of these lesions is generally positive for CD34 and negative for CD68, S100, SMA and desmin [25].

Recently, CD34, EMA and CD99 were found very useful in the diagnosis of the newly described entity "Superficial Acral Fibromyxoma" [26].

So-called Fibrohistiocytic Tumors

Histiocytic markers have limited applications in the diagnosis of soft tissue tumors with CD163 as an exception [27, 28]. True histiocytic differentiation occurs only in a few tumors, and can be identified in the lesional cells of juvenile xanthogranuloma and in true histiocytic neoplasms (true histiocytic lymphoma/sarcoma) [29]. It can also be seen in most cases of primitive myeloid tumors and in soft tissues named as extramedullary myeloid tumors or granulocytic sarcoma. Histiocyte-rich non-neoplastic lesions include necrobiotic granulomas, xanthomas, fibroxanthomas and foreign body and other granulomas. In addition, high numbers of reactive histiocytes are seen in the so-called fibrohistiocytic tumors. However, the presence of large numbers of histiocytes is not specific for fibrohistiocytic tumors as they may occur in other types of sarcomas, especially in high grade and undifferentiated tumors.

Malignant fibrous histiocytoma (MFH) is a designation used for poorly differentiated sarcomas that do not show any specific differentiation, except perhaps fibroblastic differentiation. This diagnosis is, therefore, made by exclusion of other specific diagnoses, including leiomyosarcoma, metastatic sarcomatoid carcinoma, and melanoma [30, 31]. Because this tumor does not display true histiocytic differentiation, histiocytic markers have no role in its diagnosis. In two studies employing multiple lineage markers for histiomonocytic cells, MFH cells were negative, suggesting their fibroblast-like phenotype [32, 33]. However, MFH cells often express CD68, which is not specific for histiocytes, together with SMA and CD34 [34]. It is also possible that MFHs contain higher numbers of reactive histiocytes than other sarcomas; such a high content of histiocytes has probably led previous electron microscopy studies to conclude that MFH shows histiocytic differentiation.

Among the best histiocytic markers is lysozyme. However, it does not stain all histiocytes as the lysozyme content is dependent on the functional status of the

histiocytes. Moreover, some non-histiocytic cells are considered to be rich in lysozyme. CD68 (KP1) and NKI-C3 react with most histiocytes, but it also reacts with lysosomal components in cells of any lineage. Therefore, it is positive in many lysosome-rich tumors, for example, granular cell tumors, Schwann cell tumors, melanomas, and high grade sarcomas of different phenotypes. Some carcinomas may also be CD68-positive, limiting the value of this marker, except in narrow settings [35].

Factor XIIIa, a component in the coagulation pathway, is expressed in histiocytes and related cells and has been shown in a number of fibrous and fibrohistiocytic tumors [36]. Our impression on the numerous Factor XIIIa-positive cells in the fibrohistiocytic tumors, such as MFH, is that they represent abundant non-neoplastic histiocytes that typically infiltrate these tumors.

Lipomatous Tumors

No specific markers are currently available for the diagnosis of fatty tumors. Normal fat cells and some neoplastic adipocytes are positive for S100-protein, and 1 study showed that S100 can be useful in the diagnosis of such poorly differentiated tumors as round cell liposarcoma [37]. We have found that S100 reactivity is inconsistent in fatty tumors, even in the lipogenic components; we therefore do not routinely apply this marker.

Recently, an immunohistochemical panel composed of MDM2 and CDK4 was recommended to differentiate atypical lipomatous tumor/well differentiated liposarcomas (ALT/WDLS) from benign adipose tumors and to separate dedifferentiated liposarcomas (DDLS) from poorly differentiated sarcomas [38, 39]. In these studies, majority of ALT/WDLS expressed both markers, whereas benign adipose tumors were predominantly negative. In addition, the dedifferentiated component of DDLS usually retained the expression of MDM2 and CDK4 [38].

Spindle cell lipoma and the closely related pleomorphic lipoma are relatively uncommon subcutaneous tumors typically seen in the posterior neck of older men. These lesions contain foci of bland (or pleomorphic) spindle cells which are strongly CD34-positive [40]. Often fatty tumors such as well-differentiated liposarcoma and spindle cell non-lipogenic components of fatty tumors (including some dedifferentiated liposarcoma) may show CD34 [41].

Angiomyolipoma and Related Tumors (PEComas)

Angiomyolipoma most commonly occur in the kidney, but similar tumors may also present in the retroperitoneum, skin and liver. Recently, sugar tumor of the lung and similar tumors identified in other organs have been found closely related to angiomyolipoma. It was suggested that they represent neoplasms (sometimes referred to as hamartomas) of a unique perivascular epithelioid cell population (PEComas). The lymphangioleiomyomas of lung and retroperitoneum also belong to this group [42, 43].

Immunohistochemically angiomyolipomas, lymphangiomyomas, and related tumors are distinctive and coexpress markers of smooth muscle (consistently SMA-positive, variably desmin-positive) and melanocytes (HMB-45, Melan-A, MART). Therefore, such a constellation of markers is useful in the diagnosis of angiomyolipoma-related mesenchymal tumors, especially when they occur in an unusual clinical setting [42, 44].

Smooth Muscle Tumors

Leiomyomas are typically positive for muscle actin when evaluated with the monoclonal antibody HHF-35 or with antibodies to alpha-SMA. However, both antibodies also react with myoepithelial cells and the latter also with myofibroblasts, as seen, for example, in the myofibroblast-rich nodular fasciitis. Therefore, strong SMA-reactivity itself is not diagnostic of a smooth muscle cell tumor [45]. Typical leiomyosarcomas generally show prominent actin reactivity similar to that seen in benign leiomyomas, but desmin reactivity is variable and may be absent. In our experience, approximately 70% of leiomyosarcomas are desmin positive, and the reactivity is often focal [46-48].

Newer smooth muscle markers of diagnostic interest include various isoforms of myosin, especially smooth muscle myosin. Our experience has shown that the results of antibodies to smooth muscle myosin are essentially similar to muscle actin antibodies.

Heavy molecular weight isoform of caldesmon (HCD) is a cytoskeleton-associated calmodulin and actin binding protein that is expressed in most smooth muscle tumors but not in rhabdomyosarcoma [49]. Similar to muscle actins, HCD is also expressed in myoepithelial cells but not in myofibroblasts, and it can be considered a valuable alternative marker for the diagnosis of smooth muscle tumors [50]. Calponin is yet another cytoskeleton-associated protein shared by smooth muscle cells, subsets of myofibroblasts, and myoepithelial cells. It appears to have less value in the diagnosis of smooth muscle tumors, as it is present in reactive and neoplastic myofibroblasts and curiously, in subsets of spindle cells in synovial sarcoma [49].

Neither typical leiomyomas nor leiomyosarcomas react with CD34. Some non-neoplastic, benign neoplastic, and malignant smooth muscle tumors express keratins [51, 52]. For example, myometrium commonly shows dot-like keratin reactivity with antibodies that react to keratins 8, 18 and 19, and keratin expression in myometrial cells has been confirmed by western blotting [53]. Epithelial membrane antigen expression may also occur in leiomyosarcomas; the expression of epithelial markers in 20-30% of leiomyosarcomas should be considered in the differential diagnosis of sarcomas, and spindle cell carcinomas [52].

Skeletal Muscle Tumors

Primary cutaneous rhabdomyosarcoma is extremely rare. Only scattered case reports are found in the literature [54-56]. Most rhabdomyosarcomas and rhabdomyoblastic components in other tumors are positive for desmin and muscle actins (HHF-35), but are typically negative for alpha-SMA [5, 57, 58]. Myoglobin can be demonstrated only in differentiated rhabdomyoblasts, and may be useful in the search of rhabdomyoblasts and in the verification of scattered rhabdomyoblasts. However, it is of limited value in the diagnosis of poorly differentiated rhabdomyosarcomas because such tumors, including most cases of alveolar rhabdomyosarcomas are typically negative. In our experience, the applicability of myoglobin immunostaining is also limited by the common background problems with many of the antibodies available. Cells that are not positive for desmin and actin are almost never positive for myoglobin.

MyoD1 is a skeletal muscle specific transcription factor that is located in the nucleus. MyoD1 has been shown to be a sensitive and specific adjunct for the diagnosis of paediatric rhabdomyosarcoma. Pleomorphic sarcomas in adults have been verified as rhabdomyosarcomas based on MyoD1 nuclear expression [59-61]. Cytoplasmic MyoD1 staining has also been described in rhabdomyosarcomas; however, this pattern may occur in other tumors and cannot be considered specific for rhabdomyosarcoma [62].

Many childhood rhabdomyosarcomas exhibit polyphenotypic features, as they may express keratins, neurofilaments and non-specific enolase (NSE). These features should be considered in the differential diagnosis of epithelial and keratin-positive or neural and neurofilament-positive tumors [63]. Reactivity for S100 protein commonly occurs in skeletal muscle, especially in atrophic muscle fibres, and it is therefore not surprising that rhabdomyosarcomas may also be S100 protein positive [63].

Vascular Tumors

The diagnosis of endothelial differentiation is often challenging, especially in cases of angiosarcoma showing limited vasoformation or morphologically simulating epithelial tumors.

Von Willebrand factor (VWF, also called factor VIII-related antigen) is expressed in vascular endothelial cells, megakaryocytes and platelets, and most cases of benign vascular tumors. Although it is very useful in the differential diagnosis of borderline epithelioid hemangioendotheliomas and epithelioid angiosarcomas from carcinomas, VWF is often undetectable in other types of angiosarcomas, as it is only partially conserved in malignant endothelial cells. Because the antibody to VWF also reacts with the soluble antigen present in hemorrhagic and necrotic tissues, such tissue components in VWF immunostains are often uninterpretable [64].

CD34 (the haematopoietic progenitor cell antigen) is a glycosylated transmembrane protein of unknown function, which is constitutionally expressed in haematopoietic

stem cells, most types of vascular endothelial cells, and subsets of fibroblasts, especially observed in perivascular and periadnexal locations in the skin and soft tissues. Lymphatics often show a weaker expression [64, 65]. CD34 is consistently expressed in Kaposi sarcoma, but is variably present in angiosarcomas and epithelioid hemangioendotheliomas (approximately 50%). The reactivity of CD34 in a variety of fibroblastic, lipomatous, and gastrointestinal stromal tumors and epithelioid sarcoma also limits its value as an endothelial cell marker, but does extends the application of this marker to the subtyping of other mesenchymal tumors [66].

CD31 (platelet-endothelial cell adhesion molecule 1, PE-CAM-1) is a cell surface molecule with immunoglobulin homology. CD31 is expressed in all endothelial cells, platelets and in subsets of haematopoietic cells, including haematopoietic stem cells and some histiocytes [67]. CD31 is considered the most sensitive marker for endothelial cell; however, histiocytes can be positive, which is a hidden pitfall [68]. It is present in most angiosarcomas and Kaposi's sarcomas and currently is the single most useful marker in the diagnosis of poorly differentiated angiosarcomas in terms of sensitivity and specificity. In typical cases, distinct membrane staining is observed. Also, epithelioid vascular tumors, including epithelioid hemangioendotheliomas and epithelioid angiosarcomas, are typically positive in approximately 85-95% of cases [64, 67, 69]. Reactivity with platelets causes staining in areas of thrombosis and haemorrhage. CD31 reactivity in occasional epithelial tumors has been described [70].

FLI-1 protein is a nuclear transcription factor which is frequently used in the immune-histochemical diagnosis of Ewing's sarcoma/primitive neuroectodermal tumors. It is also expressed in endothelial cells and was reported to be highly sensitive in the detection of vascular neoplasms [71, 72]. However, it is also expressed in lymphocytes which may produce a background staining and lead to the erroneous identification of intratumoural lymphocytes as endothelial cells. Moreover, its expression in other, non-endothelial tumors, limits its use as a stand-alone vascular marker [73].

Human erythrocyte-type glucose transporter protein (GLUT-1) was found to be a reliable immunohistochemical marker in distinguishing haemangiomas (GLUT-1 positive) from vascular malformations and pyogenic granuloma (GLUT-1 negative) [74, 75].

Kaposi's sarcoma is a human herpes virus-8 (HHV-8) induced vascular tumor. The 4 epidemiological forms of Kaposi's sarcoma (classic, endemic, iatrogenic and HIV-related) show nuclear expression of HHV-8 latent nuclear antigen-1 [76, 77], which is considered a highly sensitive and specific marker for differentiating Kaposi's sarcoma from other spindle cell tumors [78].

Perivascular Tumors

Hemangiopericytoma (HPC) is defined histologically, and it comprises a group of benign and borderline tumors that present in a wide variety of locations, the most common being retroperitoneum and extremities. Malignant overtly sarcomatous tumors with a hemangiopericytoma-like pattern usually represent synovial sarcomas or other type of soft tissue sarcomas. HPC differs from the normally actin-positive pericytes, because the lesional spindle cells, with rare exceptions, do not express actins [79, 80]. However, the spindle cells are typically CD34-positive but negative for desmin and keratins. Only the endothelial cells in these tumors react with CD31. Therefore, hemangiopericytoma probably is a tumor of primitive perivascular mesenchymal cells rather than tumor of differentiated pericytes.

Solitary fibrous tumor (SFT), which commonly shows hemangiopericytoma-like histologic patterns in some areas of the tumors, is immunohistochemically inseparable from hemangiopericytoma and is defined by histology. Both SFT and HPC are CD34-positive and actin and desmin-negative tumors, which probably overlap, especially when presenting in non-serosal sites [8, 10]. Some SFTs express CD99, Bcl-2 and less frequently SMA but they are consistently negative for desmin, factor XIIIa, keratin, EMA and S100 [81].

Myopericytoma is a tumor originating from perivascular myoid cells sharing features of both smooth muscle cells and glomus cells. This tumor usually displays diffuse positivity with SMA with occasional focal and weak

positivity for desmin. Immunostaining for S100, HMB45, CD34 and keratin is negative [82].

Glomus tumors are considered to be arising from modified smooth muscle cells and therefore they show a smooth muscle-like phenotype by their consistent muscle actin (HHF-35) and alpha-SMA positivity. A significant proportion of these tumors are positive for CD34 but they are consistently negative for CD31. They rarely express desmin and are negative for S100 and keratins; the latter finding is useful in the differential diagnosis from epithelial skin adnexal tumors with round cell morphology [79, 83, 84].

Schwann Cell Tumors

Benign neurofibromas are typically composed of admixed Schwannian and fibroblastic elements. The former are positive for S100 protein, whereas the latter (often an extensive component) are positive for CD34 [85]. Combined use of these 2 markers is, therefore, useful in the diagnosis of neurofibroma. According to our experience, preservation of the S100+ and CD34+ cell populations is typical in benign neurofibromas, and such a dual population is typically absent in malignant peripheral nerve sheath tumors. The differential diagnosis of diffuse neurofibroma and DFSP, both of which often show diffuse fat infiltration, is aided by the S100 protein reactivity of the former.

Benign schwannomas are composed of compact sheets of Schwann cells, variably prominent blood vessels and loose, degenerative foci often rich in histiocytes. The neoplastic spindle cell components are almost uniformly S100 protein positive, whereas CD34 is seen only in the pericapsular area and loose, degenerative areas. Schwannomas commonly express glial fibrillary acidic protein (GFAP) and are sometimes positive for keratins [86].

Additional markers expressed in Schwann cells include basement membrane components collagen type IV and laminin. Schwannomas show abundant basement membrane deposition around the thin cell processes of the Schwann cells and are typically strongly positive for basement membrane proteins, with apparent diffuse staining in histological sections [87, 88]. Granular cell tumor of soft tissues is believed to be of Schwannian derivation. This tumor is consistently S100 protein positive and also reacts with CD68 (KP1) because of its high content of lysosomes [35, 89, 90].

Malignant peripheral nerve sheath tumors (MPNSTs) can be definitively diagnosed when they occur in connection with a pre-existent neurofibroma or nerve trunk, often in connection with neurofibromatosis type 1. These tumors can be tentatively diagnosed by histologic appearance and expression of Schwannian markers, especially S100 protein. However, less than 50% of MPNSTs are S100-positive. Low grade MNPSTs show a more diffuse S-100 staining compared to high grade tumours, which tend to show a patchy and weak staining pattern [91]. In our experience, epithelioid subtypes tend to be diffusely positive for S100 [4, 92]. MNPSTs are negative for keratin, EMA, GFAP, neurofilament, desmin and CD34 [92]. Occasional cases showed focal positivity for SMA [93]. [93]. Ki67 index ranged between 5%-65% in MPNSTs, while none of the benign peripheral sheath tumors had a labelling index greater than 5% [94]. Another useful marker is the percentage of p53 expression as it ranges from 5-100% in MPNSTs and not more than 1% in benign peripheral nerve sheath tumors [94].

Epithelial sheath neuroma is a recently described entity representing a superficial dermal proliferation of enlarged nerve fibers ensheathed by squamous epithelium. The nerve fibers are immunoreactive for S100 protein, neurofilaments, CD57, and nerve growth factor receptor, whereas the perineural epithelial sheaths are positive for cytokeratins [95].

Neurothekeoma is a benign tumor of uncertain histogenesis. It has been postulated to be arising from fibroblasts/myofibroblasts [96]. These tumors are typically positive for NKI/C3, vimentin, NSE, CD10, and microphthalmia transcription factor, with occasional tumors showing focal reactivity for SMA and CD68. All tumors were negative for S100 protein, GFAP, and Melan A [96, 97]. It has to be noted that NKI/C3 is not entirely specific for neurothekeoma as it can be expressed in a wide range of histiocytic lesions and therefore correlation with the morphological picture is required [98].

Perineurial Cell Tumors

Perineuriomas are very rare soft tissue tumors that show cellular differentiation similar to perineurial (and meningeal) cells and express EMA, Glut-1 and claudin-1; they are negative for S100 protein [99, 100]. Such an IHC constellation, similar to that observed in meningiomas, has been used to identify examples of benign spindle cell and epithelioid and malignant perineuriomas [101, 102].

Paragangliomas

Paragangliomas are a group of neural neuroendocrine tumors. Most common examples of this group include pheochromocytomas of the adrenal, retroperitoneal extra-adrenal paragangliomas, carotid body, tympanic, and vagal paragangliomas. Skin is one of the rare and unusual sites for paragangliomas [103]. Although the organoid pattern is often sufficiently distinctive, it may be poorly developed in malignant variants. On the other hand, other tumors such as neuroendocrine carcinomas, smooth muscle tumors, meningiomas, and melanomas may show organoid patterns simulating those of paraganglioma.

Common to most paragangliomas is the expression of neural markers chromogranin, synaptophysin, and neuro-filaments and negativity for keratins and EMA in the chief cell component. Benign paragangliomas typically contain delicate, elongated S100-positive Schwann cell-like, so-called sustentacular cells in the periphery of the spherical organoid clusters [104]. This component may also be GFAP-positive. Analysis of malignant paragangliomas suggests common loss of the sustentacular cell component [104].

Synovial Sarcoma

The occurrence of primary cutaneous synovial sarcoma is extremely rare [105]. The biphasic malignant tumors composed of glandular and spindle cell elements in soft tissues usually represent synovial sarcomas and can usually be diagnosed without special studies. The monophasic spindle cell type is probably the most common variant of synovial sarcoma. Although the uniform pattern of spindle cell with pointed nuclei and scattered microcalcifications is highly suggestive for synovial sarcoma, differential diagnosis from nerve sheath or smooth muscle tumors may be difficult. Both the epithelial and the spindle cell components of biphasic synovial sarcoma show pancytokeratin and EMA positivity. In monophasic tumors, scattered spindle cells are positive for both markers. In contrast to haemangiopericytoma/solitary fibrous tumor CD34 is consistently negative [106].

EMA may be a more sensitive marker than keratins for monophasic and poorly differentiated synovial sarcomas, and most cases show patchy or streaky reactivity [107]. The possible, usually focal, S100 reactivity in synovial sarcoma should not be interpreted to indicate nerve sheath differentiation. Similarly, CD99 reactivity occurs in all variants of synovial sarcoma and should not lead to the diagnosis of Ewing's sarcoma and related tumors [108]. Analysis of poorly differentiated synovial sarcomas in comparison with other tumors have shown that keratin 7, typically seen in poorly differentiated as well as other synovial sarcomas, is absent in MPNSTs [109, 110].

Clear Cell Sarcoma and Metastatic Melanoma

Clear cell sarcoma of tendons and aponcuroses is a rare soft tissue sarcoma, which predominantly occurs in the distal extremities of young adults. Occasional case reports of primary cutaneous clear cell sarcoma have been reported [111, 112]. This tumor shows melanocytic differentiation and compartmentalization of tumor cells between thick fibrous septa. Clear cell sarcoma is typically variably positive for S100 protein and usually strongly positive for HMB-45, while negative for keratin and muscle cell markers [113]. Although the histologic and clinicopathologic features are distinctive, its diagnosis requires exclusion of (metastatic) melanoma.

Metastatic or bulky primary malignant melanoma is a common and often difficult problem in soft tissue diagnosis as these tumors are often non-pigmented and can show various combinations of sarcomatous spindle cell, carcinoma-like epithelioid or lymphoma-like round cell patterns. The demonstration of strong S100 protein reactivity in a malignant soft tissue tumor always necessitates consideration of malignant melanoma in the differential diagnosis.

Curiously, there remains a significant group of melanoma-like soft tissue tumors without apparent primary tumors elsewhere. They may represent primary epithelioid nerve sheath tumors, but such a diagnosis requires clinical exclusion of melanoma. Metastatic melanomas have been stated to show HMB-45-reactivity in over 90% of cases, but lack of this marker should not detract from the diagnosis of melanoma; there is some evidence that HMB-45 may be deleted in metastases [114]. New melanoma markers tyrosinase and Melan-A/MART (melanoma antigen recognized by T-cells) have been shown equally as sensitive as HMB-45, and have been detected in approximately 85% of amelanotic melanomas [114, 115]. Keratin-expression has been described in some melanomas (in our experience as often as in 10-20%), and the presence of keratins has been confirmed by western blotting [116].

Epithelioid Sarcoma

Epithelioid sarcoma is an uncommon soft tissue sarcoma that typically occurs in the distal extremities of young adults; but it may also occur in more proximal locations where it often shows large cells, sometimes with rhabdoid cytoplasm [117]. Keratins and EMA are present in most if not all cases [118, 119].

In our experience, all variants of epithelioid sarcoma typically show reactivity for EMA and low molecular weight keratins 8, 18, and 19, but usually not for keratin 7 (if present only focally). Keratins of higher molecular weight, such as K5 and K14, occur focally in the majority of tumors. A feature that was found useful when using K5/6 in differentiating epithelioid sarcoma which showed focal and weak staining from spindle cell squamous cell carcinoma which showed diffuse and strong staining [120]. Approximately 50% of epithelioid sarcomas are positive for CD34, and one-third displays muscle actin immunoreactivity. Although the biologic significance of the latter 2 findings is open, such findings are diagnostically useful. Vimentin negativity of epithelioid sarcoma has been occasionally described, but according to our experience, such a finding is very rare if heat-induced epitope retrieval is employed [121]. S100 and desmin are usually negative [122].

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