

Chapter 29

Soft Tissue and Bone Tumors

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Abstract Immunohistochemistry is a powerful adjunctive technique for the pathologic diagnosis of soft tissue and bone tumors, although some tumors still lack of specific markers. This chapter includes the questions about the immunohistochemical markers for normal soft tissue and bone, soft tissue and bone tumors, and their utility for differentiation. The questions are answered in the form of tables. The photos of selected markers are also included. New markers such as claudin-5, ERG, GAP43, INI1, MDM2, MUC4, NKX2.2, NY-ESO-1, SATB2, SOX9, SOX10, STAT6, as well as other commonly used markers are discussed.

Keywords Adamantinoma • Aggressive angiomyxoma • Alveolar soft part sarcoma • Angiomatoid fibrous histiocytoma • Angiosarcoma • Atypical fibroxanthoma • Chordoma • Clear cell sarcoma of soft parts • Dermatofibrosarcoma protuberans • Desmoplastic small round cell tumor • Epithelioid sarcoma • Ewing sarcoma • Fibromatosis • Glomangiopericytoma • Glomus tumors • Granular cell tumor • Hemangioendothelioma • Hemangiopericytoma • Inflammatory myofibroblastic tumor • Kaposi sarcoma • Langerhans cell histiocytosis • Leiomyosarcoma • Liposarcoma • Low-grade myofibroblastic sarcoma • Low grade fibromyxoid sarcoma • Malignant extrarenal rhabdoid tumor • Malignant melanotic schwannian tumor • Mammary-type myofibroblastoma myofibroma • Mesenchymal chondrosarcoma • Myoepithelial tumors • Myxofibrosarcoma • Neurofibroma • Neurothekeomas • Neuroblastoma • Nodular

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fasciitis • Notochord • Osteosarcoma • Ossifying fibromyxoid tumor of soft parts • Perineurioma • Perivascular epithelioid cell neoplasms • Phosphaturic mesenchymal tumor • Pleomorphic hyalinizing angiectatic tumor • Primitive neuroectodermal tumor • Reticulohistiocytoma • Rhabdomyosarcoma • Schwannoma • Solitary fibrous tumor • Spindle cell hemangioma • Synovial sarcoma • Undifferentiated pleomorphic sarcoma • β -catenin • Brachyury • Calponin • CD1a • CD31 • CD34 • CD99 • Chromogranin A • Claudin-1 • CDK4 • Desmin • ERG • FLI1 • GLUT1 • h-Caldesmon • HHV8 LANA • HMB-45 • INI1 • MDM2 • Melan A • MITF • MUC4 • myoD1 • Myogenin • NB84 • NKX2.2 • NY-ESO-1 • S100 • SATB2 • SOX9 • SOX10 • STAT6 • TFE3 • TLE1 • Type IV collagen • Vimentin • WT-1

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Table 29.1 Summary of applications and limitations of useful markers

Antibodies	Staining Pattern	Function	Key applications and pitfalls
AE1/AE3	C	Intermediate filaments in epithelial cells	Epithelial marker. The cocktail acidic (AE1) and basic keratins (AE3) include high and low molecular weight keratins, numbers 1–8 and 9–17 and 19. Positive in epithelioid sarcoma, synovial sarcoma, extrarenal rhabdoid tumor, and other soft tissue tumors with epithelial differentiation, some angiosarcomas and leiomyosarcomas, and sporadically other sarcomas
ALK	C+N	A tyrosine kinase receptor for the growth factor pleiotrophin	Positive in anaplastic large cell lymphoma, some large B-cell lymphomas, inflammatory myofibroblastic tumor, MPNST, leiomyosarcoma, Ewing sarcoma, and some rhabdomyosarcomas (80 % in alveolar rhabdomyosarcoma)
Bcl-2	M+C+N	A mitochondrial and microsomal protein and can inhibit apoptosis. Normally expressed by small B lymphocytes of the mantle and marginal zones and by T cells	Positive in normal T-cells and B-cell subsets, follicular derived B-cell lymphomas and many soft tissue tumors, such as solitary fibrous tumor, synovial sarcoma and GIST
Ber-EP4	M	A cell surface glycoprotein broadly distributed in epithelial cells	Expressed in all epithelial cells, except for superficial layers of squamous epithelium, hepatocytes and gastric parietal cells. Positive in carcinomas, biphasic synovial sarcoma, and some desmoplastic small round cell tumors
β-catenin	M+C+N	A component of cell-cell adhesion and Wnt signal transduction pathway	Nuclear positivity in desmoid fibromatosis (80 %), superficial fibromatoses (50 %), solitary fibrous tumor, low-grade myofibroblastic sarcoma. Widespread cytoplasmic expression in epithelial and mesenchymal cells

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Table 29.1 (continued)

Antibodies	Staining Pattern	Function	Key applications and pitfalls
Brachyury	N	A transcription factor encoded by the T gene and is essential for mesoderm formation and cellular differentiation	A diagnostic marker for chordoma
CD1a	M	MHC-related glycoprotein. Expressed in immature T cells, interdigitating reticulum cells, and Langerhans cells	Positive in lymphoblastic lymphoma and Langerhans cell histiocytosis
Calponin	C	Calcium binding protein; inhibitor of smooth muscle ATPase	Marker for smooth muscle, myofibroblasts, myoepithelial cells. Also positive in synovial sarcoma
Calretinin	C or N+C	Calcium binding protein	Positive in mesothelial cells, adipocytes, mast cells, neural cells, and sex cord tumors
CD10	M	A zinc-dependent cell membrane metalloprotein, also known as common acute lymphoblastic leukemia antigen	Positive in follicular center cells, acute lymphocytic leukemia, some renal cell carcinomas, melanoma, rhabdomyosarcoma, and many fibroblastic tumors
CD31	M+C	A membrane glycoprotein found at endothelial cell junctions and on the surface of platelets	Very sensitive and specific endothelial marker. Positive in vascular tumors and histiocytic sarcoma. Also expressed in intratumoral macrophages
CD34	C+M	A transmembrane glycoprotein. Marker for endothelial and hematopoietic progenitor cell	Positive in vascular tumors, spindle cell lipoma, many fibroblastic tumors, DFSP, neurofibroma, some smooth muscle tumors, peripheral nerve sheath tumors, GIST, solitary fibrous tumor, perineurioma, epithelioid sarcoma. Less specific and sensitive marker for vascular tumors than CD31
CD56	M+C	A cell adhesion molecule, a marker for neuroendocrine differentiation	Positive in neuroendocrine tumors, some carcinomas, and a variety of sarcomas, including ES/PNET neuroblastoma, nerve sheath tumors, synovial sarcoma, leiomyosarcoma, rhabdomyosarcoma, synovial sarcoma, and mesenchymal chondrosarcoma
CD57 (Leu7)	M	A myelin-associated glycoprotein	Marker for NK cells, T-cell subset, neuroendocrine tumors, and nerve sheath tumors. Also positive in neuroblastoma, ES/PNET, granular cell tumors, synovial sarcoma, leiomyosarcoma, some carcinomas
CD68	C+M	A glycoprotein associated with lysosomes	Marker for lysosomes. Positive in histiocytes/monocytes, benign and malignant fibrous histiocytoma, granular cell tumors, and other sarcomas, melanomas, and carcinomas
CD99	M	A cell surface glycoprotein normally expressed on thymic T lymphocytes	Positive in ES/PNET, lymphoblastic lymphoma (almost 100 % membrane positivity), synovial sarcoma, MPNST, mesenchymal chondrosarcoma, hemangiopericytoma, carcinomas, high-grade neuroendocrine carcinoma
CD117 (KIT)	C+M	Type III receptor tyrosine kinase playing a role in cell survival, proliferation, and differentiation	Marker for KIT-positive GIST. Also expressed in certain hematopoietic cells and mast cells
CD163	M	A transmembrane protein mediating the endocytosis of haptoglobin-hemoglobin complexes	A specific marker for monocytes and macrophages. Positive in Rosai-Dorfman disease, histiocytic sarcoma, Langerhans cell histiocytosis, AML with monocytic differentiation
CD207 (Langerin)	M	A type II membrane-associated C-type lectin known to be expressed exclusively by Langerhans cells	A marker for Langerhans cell histiocytosis
CDK4	N	A catalytic subunit of the protein kinase complex that is important for cell cycle G1 phase progression	Positive in well and dedifferentiated liposarcoma, some cases of MPNST, myxofibrosarcoma, and embryonal rhabdomyosarcoma. Lipoma, pleomorphic liposarcoma, and myxoid liposarcoma are usually negative for both MDM2 and CDK4
Chromogranin A	C	An acidic glycoprotein located in neurosecretory granules	Positive in epithelial neuroendocrine tumors (carcinoid/ carcinomas), and paraganglioma
CK5/6	M+C	Basic keratins, an epithelial marker	Positive in squamous and basal cells, squamous cell carcinoma, urothelial carcinoma, and basal cell carcinoma
CK7	M+C	Basic, low molecular weight keratin, an epithelial marker	Positive in many carcinomas and epithelial elements of synovial sarcoma

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Table 29.1 (continued)

Antibodies	Staining Pattern	Function	Key applications and pitfalls
CK8 (CAM5.2)	C	Low molecular weight keratin, a epithelial marker	Positive in most carcinomas, synovial sarcoma, and epithelioid sarcoma
CK14	C	Low molecular weight keratin, a epithelial marker	Positive in carcinoma with stratified epithelial differentiation and biphasic synovial sarcoma
CK17	C	Acidic type I cytokeratin, a epithelial marker	Positive in some carcinomas and adamantinoma, and focally in biphasic synovial sarcoma
CK19	C	Low molecular weight keratin, a epithelial marker	Positive in most carcinomas and synovial and epithelioid sarcoma
CK20	M+C	Low molecular weight keratin, a epithelial marker	Positive in most GI carcinomas and some other carcinomas
D2-40 (podoplanin)	M+C	A transmembrane sialoglycoprotein	Positive in mesothelial cells, lymphatic endothelial cells, seminomas, follicular dendritic cell sarcoma, tumor of skin adnexa, and many carcinomas. A useful marker to detect angiolymphatic invasion of tumors
Desmin	C	Intermediate filament related to the sarcomere	Very sensitive and specific marker for smooth muscle and striated muscle tumors. Also positive in myoid cells and some reticulum cells of the lymph node, submesothelial fibroblasts, desmoid tumors, DSRCT, tumors with heterologous myoid differentiation (MPNST, rhabdoid tumor), tumors with myofibroblastic features, PEComas, ossifying fibromyxoid tumors, and angiomatoid fibrous histiocytomas
DOG-1	M	Also known as Anoctamin-1 (Ano-1) and transmembrane protein 16A (TMEM16A)	Marker for GIST
Claudin-1	C	One of transmembrane proteins of the tight junctions, a marker for epithelial and perineurial cells	Positive in perineurioma. Variable expression in neurofibroma, low-grade fibromyxosarcoma synovial sarcoma, epithelioid sarcoma, and ES/PNET
Claudin-5	C	One of transmembrane tight junction (zonula occludens) proteins contributing to epithelial and endothelial barrier function	Positive in vascular tumors, carcinomas, biphasic synovial sarcoma, and extraskeletal myxoid chondrosarcoma. A sensitive, but not specific endothelial marker
EAAT4	C	EAAT4 is a member of the high-affinity glutamic acid and neutral amino acid transporter family	Positive in ossifying fibromyxoid tumor of soft parts
EBNA1	N	EBV nuclear antigen	Positive in EBV-associated smooth muscle tumors or some lymphomas
E-cadherin	M	The major calcium dependent cell adhesion molecule of epithelial cells	Expression by carcinomas is inversely proportional to the degree of differentiation, positive in sarcoma with epithelioid differentiation, such as synovial sarcomas
EMA (MUC1)	M+C	One of human milk fat globule proteins, an epithelial marker	Positive in carcinomas, mesothelioma, meningioma, a subset of lymphomas, synovial sarcoma, epithelioid sarcoma, low-grade fibromyxoid sarcoma, perineurioma, myoepithelial tumors, epithelioid benign fibrous histiocytoma, some plasmacytomas, chordoma, and angiomatoid fibrous histiocytomas
ER	N	Estrogen receptor	Positive in breast carcinoma, cellular angiofibroma, angiofibrosarcoma and female deep smooth muscle tumors
ERG	N	An ETS-family transcription factor and regulates endothelial cell differentiation and angiogenesis	Highly sensitive and specific marker for endothelial cells. Positive in endothelial neoplasms, prostatic carcinoma (50%), and rare cases of Ewing sarcoma, AML. It is the most specific and sensitive marker for endothelial cells. Can be positive in epithelioid sarcoma
Factor XIIIa	C	Subunit of plasma clotting factor XII	A marker for dermal dendrocyte. Positive in intratumoral histiocytes, present in greater quantity in benign fibrous histiocytoma than in DFSP
FGF23	C	A member of the fibroblast growth factor (FGF) family which is responsible for phosphate metabolism	Positive in phosphaturic mesenchymal tumor. Information on specificity is limited

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Table 29.1 (continued)

Antibodies	Staining Pattern	Function	Key applications and pitfalls
FLI1	N	Nuclear transcription factor involved in cell proliferation	Positive in vascular tumors, ES/PNET, lymphoblastic lymphoma, subset of wide range of mesenchymal tumors, carcinomas, and melanomas
GAP43	C	An intracellular growth-associated protein, plays critical role in guiding axonal growth and normal central nervous system development	Positive in MPNST, schwannoma, neurofibroma, desmoplastic melanoma. Rare cases of leiomyosarcomas, spindle cell melanoma, synovial sarcoma, and clear cell sarcoma are positive
GFAP	C	One of the major types of intermediate filament in astrocytes and ependymal cells	Schwann cell, myoepithelial cells and chondrocytes may express GFAP. Positive in some nerve sheath tumors (especially schwannomas), sustentacular cells of paragangliomas, and myoepithelial tumors
GLUT1	C+M	Major glucose transporter at epithelial and endothelial tissue	Positive in perineurioma and infantile hemangiomas but absent in other pediatric vascular tumors, including vascular malformations. Also positive in chordoma, epithelioid sarcoma, leiomyosarcoma, synovial sarcoma, ES/PNET, undifferentiated pleomorphic sarcoma, and GIST
h-Caldesmon	C	A cytoskeleton-associated protein which regulates cellular contraction	Positive in smooth muscle tumors, glomus tumors, GIST and myopericytomas. Negative in myofibroblasts
HHV8 LANA	N	Latent nuclear antigen of human herpes virus type 8	Positive in Kaposi's sarcoma, primary effusion lymphoma, and Castleman disease
HMB45	C	Antibody recognizes the antigen gp100 on melanosomes	Positive in melanoma, cellular blue nevus, and PEComas, including angiomyolipoma
INI1/SMARCB1	N	A member of the SWI/SWF chromatin-remodelling complex, encoded by a putative tumor suppressor gene, normally expressed in all tissues	Loss of nuclear expression in epithelioid sarcoma, rhabdoid tumor, epithelioid MPNST, atypical teratoid/rhabdoid tumor, extraskeletal myxoid chondrosarcoma, pediatric myoepithelial carcinoma, and subset of myoepithelial carcinoma
Ki-67 (MIB1)	N	Nuclear proliferation marker; Expression in cells in the G1, M, G2, and S phase of the cell cycle except G0 phase	Marker for proliferation index. Ki-67 index (the number of Ki-67-positive tumor cells/10 HPF) positively correlated with mitotic count, cellularity and the histological grade. Threshold values vary by tumor
Microtubule-associated protein-2 (MAP-2)	C	MAP-2 functions to stabilize and promote the formation of microtubules which are important for maintenance of specialized intracytoplasmic secretory functions and complex cell shapes	A sensitive and specific marker of neuroblastoma. Other tumors could express (usually rarely) MAP-2 including AML, angiosarcoma, carcinosarcoma, dermatofibroma sarcoma protuberans, clear cell sarcoma, ectomesenchymoma, endometrial stroma sarcoma, fibroma, GIST, glomus tumor, giant cell tumor of bone, juvenile xanthogranuloma, Kaposi sarcoma, leiomyosarcoma, liposarcoma, MPNST, nodular fasciitis, pigmented villonodular synovitis, rhabdomyosarcoma, solitary fibrous tumor/hemangiopericytoma, synovial sarcoma, thyroid papillary carcinoma, and Wilms tumor
MDM2	N	A protein functions both as an E3 ubiquitin ligase that recognizes the N-terminal trans-activation domain (TAD) of the p53 tumor suppressor and an inhibitor of p53 transcriptional activation	Positive in well and dedifferentiated liposarcoma, some cases of MPNST, myxofibrosarcoma, and embryonal rhabdomyosarcoma. Lipoma, pleomorphic liposarcoma, and myxoid liposarcoma are usually negative for both MDM2 and CDK4
Melan-A (MART1)	C	An antibody recognizes melanoma antigen, a marker for melanosomes	Positive for melanoma and PEComas
MITF	N	Transcription factor involved in the development of melanocytes and regulation of melanin synthesis, a nuclear melanocytic marker	Positive in melanoma, clear cell sarcoma, PEComas, histiocytes, and osteoclasts
MOC31	M	A glycoprotein in epithelium, but absent on mesothelial tissues	Positive in (adeno)carcinomas and a subset of squamous cell carcinoma negative in mesothelium, positive in DSRCT
MSA	C	Contractile microfilament proteins	Marker for smooth muscle and striated muscle tumors, and myofibroblastic and myoepithelial differentiation

(continued)

Table 29.1 (continued)

Antibodies	Staining Pattern	Function	Key applications and pitfalls
MUC4	C	A high-molecular weight transmembrane glycoprotein is normally expressed on many epithelial surfaces, where it is presumed to serve a protective role cell proliferation and survival	100 % low-grade fibromyxoid sarcomas, 80 % sclerosing epithelioid fibrosarcomas, and 30 % of monophasic synovial sarcomas are positive
MyoD1	N	Transcription factor, member of the MyoD family, regulating skeletal muscle differentiation	Present in immature skeletal muscle cells. Specific marker for rhabdomyosarcoma. Only nuclear staining is specific for skeletal muscle differentiation. Also positive in tumors with rhabdomyoblastic differentiation. Cytoplasmic staining has no diagnostic significance
Myogenin	N	Transcription factor, member of the MyoD family involved in skeletal muscle development and repair	Present in immature skeletal muscle cells. Specific marker for rhabdomyosarcoma. Cytoplasmic staining is not specific for skeletal muscle differentiation. Also positive in other tumors with rhabdomyoblastic differentiation
NB84	C	An antibody raised against an antigen from human neuroblastoma tissue	A highly sensitive marker for neuroblastoma. Also positive in some cases of ES/PNET, rhabdomyosarcomas, esthesioneuroblastomas, DSRCT, and Wilms tumor. More sensitive but less specific than synaptophysin
NKI/C3	C	A monoclonal antibody that recognizes a melanoma-associated antigen which is located in the cells with a large population of melanosomes	Positive in melanocytic lesions, fibrohistiocytic tumors including juvenile xanthogranuloma, atypical fibroxanthoma, atypical fibroxanthoma, cellular fibrous histiocytoma, reticulohistiocytoma and xanthoma, granular cell tumors, cellular neurothekeoma, and some carcinomas
NFP	C	Neurofilament protein, a major component of the cytoskeleton of neurons and axons	A marker for neurons and axonal processes except for olfactory sensory neurons. Positive for neuroblastic tumors, paragangliomas/pheochromocytomas, and a subset of neuroendocrine tumors, and Merkel cell carcinoma. NF68 is more prevalent than medium (NF160) and high (NF200) molecular weight neurofilament proteins
NKX2.2	N	A member of the NK2 family of transcription factors and plays a critical role in development and differentiation in the central nervous system and gastrointestinal/pancreatic endocrine cells	93 % of Ewing sarcoma/PNET show diffuse staining. Less than 10 % of non-Ewing sarcomas are positive, including neuroblastomas, small cell carcinoma, mesenchymal chondrosarcoma, and malignant melanoma
NSE	C	Neuron specific enolase, a marker for neuronal cells and cells with neuroendocrine differentiation	Low specificity. Also reacts with smooth muscle cells. Additional markers are always needed to support a diagnosis of neuroendocrine or neural tumor
NY-ESO-1	C	A member of the CT(cancer/testis) family encoded by CTAG1B gene at Xq28, involved in germ cell self-renewal or differentiation	90 % of myxoid/round cell liposarcomas are positive. Other myxoid tumors are negative. But a variety of carcinomas, melanoma, and neuroblastoma are positive
Osteocalcin	C	One of the most prevalent noncollagenous intraosseous proteins made by osteoblasts, a marker for osteoblastic differentiation	Monoclonal antibodies against osteocalcin have about 70 % sensitivity and almost total specificity for osteoblastic differentiation. Polyclonal antibodies show cross-reactivity with fibroblasts
Osteonectin	Extracellular space, extracellular matrix, basement membrane	A protein made by osteoblasts and functions in regulating the adhesion of osteoblasts and platelets to their extracellular matrix and early stromal mineralization. Marker for osteoblastic differentiation	Positive in osteosarcoma (90 %), but the specificity is relatively low (54 %). Fibroblasts, vascular pericytes, endothelia, chondrocytes, some epithelial cell, and nerves also express osteonectin-associated epitopes
Protein Gene Product 9.5 (PGP 9.5)	C	A member of the ubiquitin hydrolase family of proteins, expressed in neural and neuroendocrine cells	A sensitive neural/nerve sheath marker, but specificity is low

(continued)

Table 29.1 (continued)

Antibodies	Staining Pattern	Function	Key applications and pitfalls
PR	N	Progesterone receptor	Positive in breast carcinoma, cellular angiofibroma, angiofibrosarcoma, vulval nerve sheath tumor, aggressive angiofibrosarcoma, and female deep smooth muscle tumors
PRKAR1A	C	Carney complex–associated tumor suppressor gene product	Loss of heterozygosity and mutations of PRKAR1A in a variety of Carney complex–associated neoplasms, including malignant melanotic schwannoma, pancreatic tumors, and pigmented epithelioid melanocytoma. One third of malignant melanotic schwannian tumors show loss of PRKAR1A expression
PROX1	N	A nuclear transcription factor, functions in lymphatic development	Positive in hemangioma, lymphangioma (100%), other vascular tumors, ES/PNET, paraganglioma, synovial sarcoma, and some carcinomas
SATB2	N	A nuclear matrix protein encoded by SATB2 gene on 2q33, important for osteoblastic differentiation	Positive in bone and soft tissue tumor with osteoblastic differentiation, rare cases of other sarcomas, including unclassified pleomorphic sarcoma, dedifferentiated liposarcoma, MPNST, synovial sarcoma can be positive. 85% colorectal carcinomas are positive
S100	N+C	A calcium binding protein. Marker for Langerhans cells, myoepithelial cells, melanocytes, chondrocytes, schwann cells, and adipocytes	Positive in benign and malignant nerve sheath tumors, melanoma, some adipocytic tumors, chondrocytic tumors, ossifying fibromyxoid tumor, myoepithelial tumors, Langerhans cell histiocytosis, histiocytic sarcoma, and chordoma
SMA	C	A microfilamentous contractile polypeptide	Positive for smooth muscle, myofibroblasts, myoepithelial cells, and tumors originated from these cells
SMM-HC	C	Smooth muscle myosin heavy chain, a cytoplasmic structural protein and a major component of the contractile apparatus in smooth muscle cells	Positive in smooth muscle, myofibroblasts, and myoepithelial cells
SOX9	N	A transcription factor functions during chondrocyte differentiation	Sensitive marker for cartilaginous differentiation. Also positive in cartilage elements of mesenchymal chondrosarcoma. Information on specificity is limited
SOX10	N	A member of the sex-determining region Y-related HMG-box family, important for differentiation, maturation, and maintenance of schwann cells and melanocytes	Marker for neural crest stem cell Positive in melanoma, peripheral nerve sheath tumors, clear cell sarcoma, granular cell tumor, sustentacular cells of paraganglioma/pheochromocytoma, a subset of carcinoid tumors, myoepithelial tumors, and subset of salivary gland neoplasms, and breast carcinomas
STAT6	N	A member of STAT family of transcription factors, important for normal cellular process, embryonic development, innate and adaptive immune function, regulation of cell differentiation, growth, and apoptosis	Almost (98%) all solitary fibrous tumors are positive. 14% of dedifferentiated liposarcoma are positive
Succinate dehydrogenase complex	C	Enzyme complex composed of four subunit proteins (A to D) involved in the oxidation of succinate to fumarate in the citric acid cycle and the electron transport chain	Defects in succinate dehydrogenase complex (as detected by loss of SDHB immunostaining) in subset of GIST, pheochromocytoma, and paraganglioma
Synaptophysin	C	Synaptic vesicle membrane protein. Present in small neurosecretory vesicles of neuroendocrine and neural cells	A marker for neuroendocrine differentiation. Positive in neuroendocrine tumors, paraganglioma, and neuroblastoma
TFE3	N	Product of ASPL-TFE3 gene fusion due to unbalanced translocation, der(17) t(X;17)(p11.2;q25)	A sensitive and specific marker for alveolar soft part sarcoma. Also positive in translocation-type renal cell carcinoma, granular cell tumors, some PEComas, and subset of epithelioid hemangioendotheliomas. Only nuclear staining is diagnostic
TLS/EWS-Chop chimeric oncoproteins	N	Fusion oncoproteins of t(12;22)(q13;q11-12) and t(12;22)(q13;q12) translocations	A marker for myxoid/round cell liposarcoma

(continued)

Table 29.1 (continued)

Antibodies	Staining Pattern	Function	Key applications and pitfalls
TLE1	N	A transcriptional corepressor that inhibit Wnt signaling and other cell fate determination signals, and so have an established role in repressing differentiation	Highly sensitive for synovial sarcoma. Rarely positive in other soft tissue tumors including MPNST, fibrosarcoma, and solitary fibrous tumor are positive
Tyrosinase	C	An enzyme involved in the production of melanin	Positive in melanocytic neoplasms, clear cell sarcoma, and angiomyolipoma
Type IV collagen	C	A type of collagen found primarily in the basal lamina	Pericellular expression in glomus tumor
Vimentin	C	Intermediate filament of cytoskeleton expressed in all mesenchymal cells	Positive in most sarcomas, melanoma, some carcinomas and lymphomas, but negative in alveolar soft part sarcoma and perivascular epithelioid cell neoplasms. It is a useful control marker
vWF	C	A large glycoprotein synthesized by endothelial cells and megakaryocytes and involves in hemostasis	Positive for vascular tumors, such as hemangioma and hemangioendotheliomas. Low sensitivity in poorly differentiated vascular tumors. Can be found in zones of tumor necrosis and hemorrhage
VEGFR3	M	A transmembrane tyrosine kinase	Positive in a variety of vascular tumors, including Kaposi sarcoma kaposiform and Dabska-type hemangioendothelioma, angiosarcoma, some carcinomas and sarcomas
WT-1	C+N	A transcription factor that contains four zinc finger motifs at the C-terminus and a proline/ glutamine-rich DNA-binding domain at the N-terminus, important for normal development of the urogenital system	Positive in DSRCT, Wilms tumor, mesothelioma, ovarian serous carcinoma

C cytoplasmic staining, M membranous staining, N nuclear staining, *DFSP* dermatofibrosarcoma protuberans, *DSRCT* desmoplastic small round cell tumor, *ES/PNET* Ewing's sarcoma/primitive neuroectodermal tumor, *GIST* gastrointestinal stromal tumor, *MPNST* malignant peripheral nerve sheath tumor, *PEComas* perivascular epithelioid cell tumors

References: [1–177]

Table 29.2 Markers positive for normal soft tissue and bone

Tissue	Markers positive
Adipocyte	Vimentin, S100 (variable), calretinin
Chondrocyte	S100, SOX9
Endothelium	Vimentin, CD31, CD34, vWF, FLI-1, CK8, CK18, ERG, prox 1, thrombomodulin, UEAI, D2-40 (lymphatic endothelium)
Fibroblast	Vimentin, CD10, CD99
Langerhans' cell	S100, CD1a, CD207
Myofibroblast	Desmin, MSA, vimentin (varies)
notochord	EMA, keratins, S100 (varies)
Osteoblast	CD56, vimentin
Osteoclast	CD68, MITF, vimentin
Perineurial cell	Claudin-1, GLUT1, EMA
Smooth muscle	Desmin, SMA, MSA, NSE
Skeletal muscle	Vimentin, desmin, myoglobin, CD56, GFAP
Schwann cell	Vimentin, CD56, CD57, GAP43, S100
Synovial cell	CD68, clusterin
Nerve	CD34, Vimentin (fibroblasts), SOX10, GAP43, S100 (Schwann cells), EMA (perineurial cells)

Adipocytic Tumors

Table 29.3 Markers for spindle cell lipoma/pleomorphic lipoma

Antibody	Literature
Vimentin	+
CD34	+
Bcl-2	+
S100	– or +
MDM2	– or + (atypical examples may show nuclear positivity)
CDK4	– or + (atypical examples may show nuclear positivity)
SMA	–
Desmin	–

Note: “+”, usually greater than 70 % of cases are positive; “–”, less than 5 % of cases are positive; “+ or –”, usually more than 50 % of cases are positive; “– or +”, less than 50 % of cases are positive; *ND* no data, *C* cytoplasmic staining, *M* membranous staining, *N* nuclear staining

S100 is expressed in mature lipocytes and not expressed in spindle cells and floret-like giant cells

CD34 is positive in spindle cells and pleomorphic cells, but rarely positive in S100 positive cells

References: [5–8]

Table 29.4 Markers for well-differentiated liposarcoma/dedifferentiated liposarcoma

Antibody	Literature
Vimentin	+
CD34	+ Variable
MDM2	+ Nuclear positivity in varying numbers of cells
CDK4	+
S100	+ Variable
p16	+

CD34 is focally positive in spindle cells and negative in lipoblasts

MDM2 and CDK4 are positive in both lipogenic and non-lipogenic components. Coexpression of MDM2 and CDK4 is seen in more than 90 % of cases. A subset of malignant peripheral nerve sheath tumor, myxofibrosarcoma, and rhabdomyosarcoma are positive for MDM2 and CDK4

Identification of MDM2 gene amplification by fluorescence in situ hybridization (FISH) is more specific for well-differentiated and dedifferentiated liposarcoma than immunohistochemistry

S100 is positive in lipogenic component

References: [8–13]

Table 29.5 Markers for myxoid/round cell liposarcoma

Antibody	Literature
TLS/EWS-CHOP chimeric oncoproteins	+
NY-ESO-1	+
S100	+
MDM2	– or +
CDK4	–
CD34	–

Note: 95 % of myxoid/round cell liposarcomas are positive for NY-ESO-1, while other lipomatous tumors and myxoid tumors including myxoma, myxoid chondrosarcoma, myxofibrosarcoma, and low-grade fibromyxoid sarcoma are usually negative for this marker

Occasional cases of myxoid liposarcoma are positive for MDM2

References: [14–17]

Fibroblastic and Fibrohistiocytic Tumors

Table 29.6 Markers for nodular fasciitis

Antibody	Literature
SMA	+
MSA	+
Calponin	+
CD68	+
Desmin	–
h-Caldesmon	–
S100	–
CD34	–
β-catenin	–

Note: CD68 is expressed in the histiocytes and osteoclast-like giant cells, occasionally in the spindle cells

References: [3, 18]

Table 29.7 Markers for palmar and plantar (superficial) fibromatosis

Antibody	Literature
Vimentin	+
SMA	+ Focal
Desmin	+ Focal
β-catenin	– or + rare nuclear positivity
CD34	–
Keratins	–
EMA	–
S100	–

References: [1, 2, 19, 20]

Table 29.8 Markers for deep fibromatosis

Antibody	Literature
SMA	+
Desmin	+
β-catenin	+
CD34	–
S100	–
Keratins	–
EMA	–
CD117	–

Note: Only nuclear staining for β-catenin is specific

References: [19, 20]

Table 29.9 Markers for fibrous hamartoma of infancy

Antibody	Literature
Bcl-2	+
CD34	+
S100	+
SMA	+ or –
CD31	–
D2-40	–
HMB-45	–

Reference: [21]

Table 29.10 Markers for Inflammatory myofibroblastic tumor/inflammatory fibrosarcoma

Antibody	Literature
Vimentin	+
MSA	+
SMA	+
Calponin	+
Desmin	+
ALK	+ or –
Keratins	– or +
CD68	– or +
MDM2	– or +
Myogenin	–
h-Caldesmon	–
S100	–
CD117	–
EMA	–

Note: Keratin is expressed in 70–90 % of lesions of genital/urinary tract

A subset of rhabdomyosarcoma, MPNST, neuroblastoma and lung adenocarcinoma are positive for ALK

References: [1, 22–26]

Table 29.11 Markers of myofibroma/myofibromatosis

Antibody	Literature
Vimentin	+ (all cells)
SMA	+ (myofibroblastic elements)
MSA	+ (myofibroblastic elements)
S100	–
EMA	–
Keratin	–
Desmin	–

References: [3, 27]

Table 29.12 Markers for angiomyofibroblastoma

Antibody	Literature
Vimentin	+
Desmin	+
ER	+
PR	+
CD34	– or +
SMA	–
Keratin	–
S100	–

Note: In postmenopausal women, desmin staining may be reduced or absent

References: [28–32]

Table 29.13 Markers for cellular angiofibroma

Antibody	Literature
Vimentin	+
ER	+
PR	+
Desmin	+ or –
CD34	+ or –
SMA	– or +
S100	–
EMA	–
Keratin	–

Note: ER/PR are expressed more often in female than in male

References: [3, 33]

Table 29.14 Markers of mammary-type myofibroblastoma

Antibody	Literature
Desmin	+
CD34	+
CD10	+
CD99	+
Bcl2	+
ER	+
PR	+
AR	+
SMA	– or +

References: [3, 34]

Table 29.15 Markers for myxoinflammatory fibroblastic sarcoma

Antibody	Literature
Vimentin	+
D2-40	+
CD34	+ or –
Keratin	– or + focal
CD68	– or + focal
SMA	– or + focal
Desmin	– or + focal
S100	– or + focal
EMA	– or + focal
Myogenin	–
CD30	–
CD15	–
CD20	–
CD3	–

References: [3, 35, 36]

Table 29.16 Markers for low-grade myofibroblastic sarcoma

Antibody	Literature
Desmin	+ or –
SMA	+ or –
Calponin	+ or –
HHF35	– or +
Fibronectin	– or +
S100	–
Keratin	–
h-Caldesmon	–
CD34	–

References: [3, 37]

Table 29.17 Markers for low-grade fibromyxoid sarcoma/spindle cell tumor with giant rosettes

Antibody	Literature
MUC4	+
Vimentin	+
EMA	+
MSA	– or +
SMA	– or +
Desmin	–
S100	–
β -catenin	–

Note: MUC4 is a highly sensitive and relatively specific marker for low-grade fibromyxoid sarcoma. 100 % of low-grade fibromyxoid sarcomas are positive for MUC4

Other positive MUC4 tumors include 90 % of synovial sarcoma (predominantly glandular component) 78 % of sclerosing epithelioid fibrosarcoma and a subset of ossifying fibromyxoid tumors, epithelioid gastrointestinal stromal tumors, and myoepithelial carcinoma

No MUC4 expression has been seen in alveolar soft part sarcoma, angiosarcoma (epithelioid), clear cell sarcoma, desmoid fibromatosis, epithelioid hemangioendothelioma, epithelioid sarcoma, intramuscular/cellular myxoma leiomyosarcoma, MPNST, PEComa, perineurioma, and solitary fibrous tumor

References: [38–40]

Table 29.18 Markers for myxofibrosarcoma

Antibody	Literature
Vimentin	+
MSA	– or + focal
SMA	– or + focal
MDM2	– or +
CDK4	– or +
CD34	– or +
S100	–
Desmin	–
CD68	–

Note: Some superficial myxofibrosarcomas are positive for CD34

References: [41–43]

Table 29.21 Markers for atypical fibroxanthoma

Antibody	Literature
CD10	+
CD99	+
CD168	+
CD68	+ or –
p63	– or +
Factor XIIIa	– or +
SMA	– or +
S100	– or +
NKI/C3	– or +
Desmin	–
CD34	–
Keratin	–
EMA	–

References: [46, 47]

Fibrohistiocytic tumors

Table 29.19 Markers for benign fibrous histiocytoma

Antibody	Literature
CD163	+
CD68	+
Factor XIIIa	+
SMA	+ or –
NKI/C3	+ or –
Desmin	–
Keratin	–
S100	–
CD34	–

Note: CD68 is expressed in histiocytes

References: [1–4, 174]

Table 29.20 Markers for juvenile xanthogranuloma and reticulohistiocytoma

Antibody	Literature
CD31	+
CD68	+
CD163	+
Factor XIIIa	+
NKI/C3	+ or –
CD1a	–
S100	–

Note: Histiocytes are negative for factor XIIIa in multicentric reticulohistiocytosis

References: [44, 45, 174]

Table 29.22 Markers for dermatofibrosarcoma protuberans/giant cell fibroblastoma

Antibody	Literature
CD34	+
CD31	–
Factor XIIIa	–
Desmin	–
S100	–
EMA	–

References: [20, 48, 49]

Table 29.23 Markers for angiomatoid (malignant) fibrous histiocytoma

Antibody	Literature
Vimentin	+
Calponin	+
EMA	+ or –
Desmin	+ or –
CD99	+ or –
CD68	– or +
SMA	– or +
MSA	– or +
h-Caldesmon	–
Myogenin/MyoD1	–
Cam5.2	–
S100	–
CD21	–
CD35	–
Lysozyme	–
CD31	–
CD34	–

Note: Rare cases (3 %) are positive for caldesmon. Rare cases showed rare S100-positive tumor cells

More than 60 % of angiomatoid malignant fibrous histiocytomas coexpress desmin, EMA, and CD68

References: [50–53]

Table 29.24 Markers for plexiform fibrohistiocytic tumor

Antibody	Literature
Vimentin	+
SMA	+
CD68	+
Desmin	-
CD34	-
S100	-
NKI/C3	-

Note: CD68- Positive for multinucleated giant cells and histiocyte-like cells

SMA- Positive for spindle cells

References: [54–56]

Table 29.25 Markers for giant cell tumor of soft tissue

Antibody	Literature
Vimentin	+
CD68	+
CD163	+
SMA	+ variable
Desmin	-
CD34	-
CD31	-
Cytokeratin	-
S100	-

Note: Both mononuclear cells and multinucleated giant cells are positive for CD68. Only mononuclear cells are positive for CD163

References: [3, 57]

Table 29.26 Markers for undifferentiated pleomorphic sarcoma (pleomorphic malignant fibrous histiocytoma)

Antibody	Literature
Vimentin	+
MDM2	+
CDK4	+
SMA	- or +
Desmin	- or + focal
Keratins	-
S100	-
h-Caldesmon	-
CD45	-
CD20	-
CD30	-

References: [1–4, 59, 60]

Smooth Muscle Tumors

Table 29.27 Markers for leiomyoma and leiomyosarcoma

Antibody	Literature
Desmin	+
SMA	+
MSA	+
Calponin	+
h-Caldesmon	+
SMM-HC	+
PR	+
ER	+ or -
S100	- or +
Keratin	- or +
EMA	- or +
CD34	- or +

Note: ER and PR- Positive in leiomyoma of deep soft tissue (Müllerian type tumors) and vulva in female

Figure 29.1

References: [61–63]

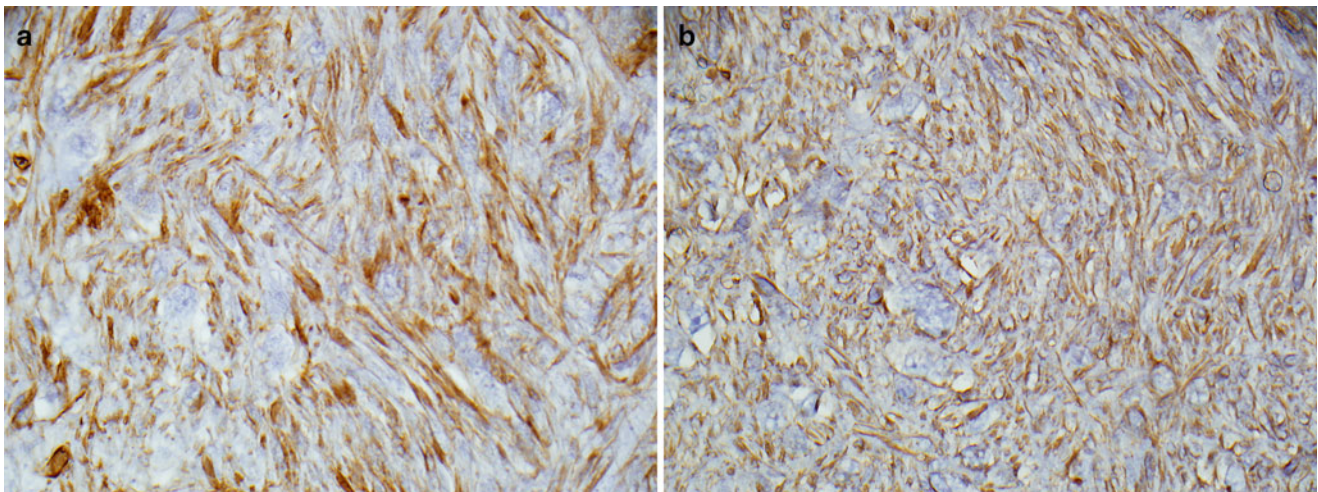


Fig. 29.1 (a) Leiomyosarcoma shows positive staining for desmin, (b) Leiomyosarcoma shows positive staining for h-caldesmon

Table 29.28 Markers for EBV-associated leiomyosarcoma

Antibody	Literature
Desmin	+
SMA	+
MSA	+
Calponin	+
h-Caldesmon	+
SMM-HC	+
EBNA-1	+
BZFL1	+
EA-D	+
VCA	+
S100	-
Keratin	-
EMA	-
CD34	-

Note: EBV RNA in situ hybridization shows nuclear staining in the tumor cells

References: [3, 64]

Skeletal Muscle Tumors

Table 29.29 Markers for rhabdomyoma

Antibody	Literature
Desmin	+
MSA	+
Myoglobin	+
p63	+
Vimentin	- or +
SMA	-
S100	-
GFAP	-
Keratin	-
EMA	-
CD68	-

Note: p63 immunostain shows cytoplasmic staining in the skeletal muscle cells

References: [65, 66]

Table 29.30 Markers for rhabdomyosarcoma

Antibody	Literature
Desmin	+
MSA	+
Myogenin	+
MyoD1	+
p63	+
Myoglobin	- or +
SMA	- or + focal
NSE	- or + focal
Keratins	- or + focal
FLI-1	-

Note: p63 immunostain shows cytoplasmic staining in the skeletal muscle tumor cells

Desmin is negative in undifferentiated cells

MyoD1 and myogenin are highly sensitive and specific markers for rhabdomyosarcoma. Only nuclear staining is specific

Epithelioid rhabdomyosarcoma can show focal or rare positivity for keratins

Figure 29.2

References: [66–71]

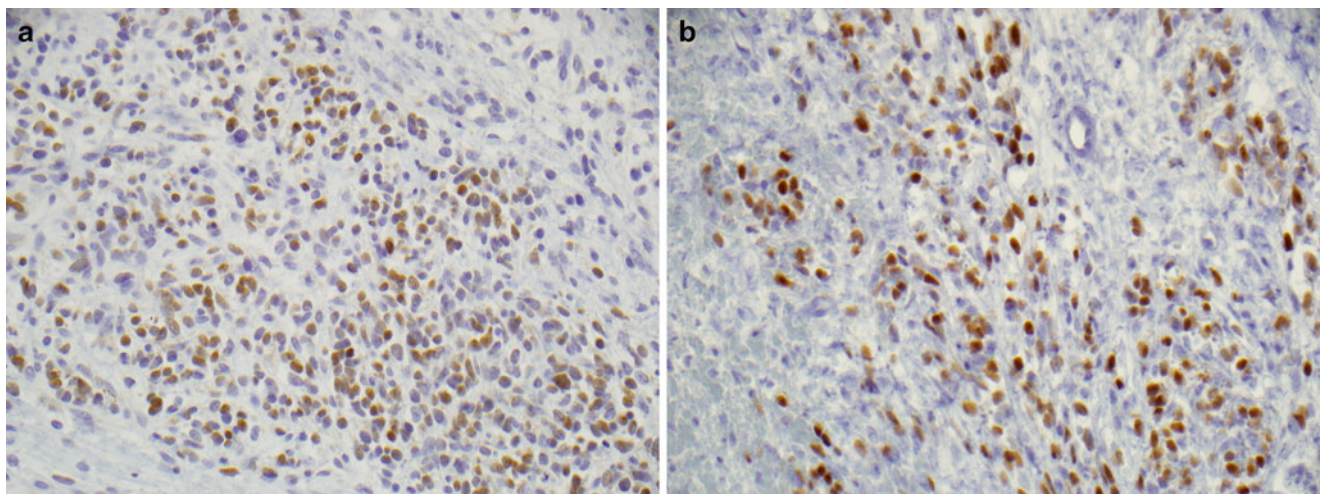


Fig. 29.2 (a) Rhabdomyosarcoma shows positive staining for MyoD1, (b) Rhabdomyosarcoma shows positive staining for myogenin

Tumors of Perivascular Cells

Table 29.31 Markers for hemangiopericytoma (HPC)/solitary fibrous tumor (SFT) of soft tissue

Antibody	Literature
STAT6	+
Vimentin	+
CD34	+
CD99	+
Bcl-2	+
CD10	+ or -
β -catenin	- or +
EMA	- or +
SMA	- or +
TLE1	- or +
CD31	-
Keratin	-
Desmin	-
CD117	-
S100	-

Note: 98 % of SFTs are positive for STAT6; dedifferentiated liposarcomas (14 %) can show positivity for STAT6

Figure 29.3

References: [14, 72–79]

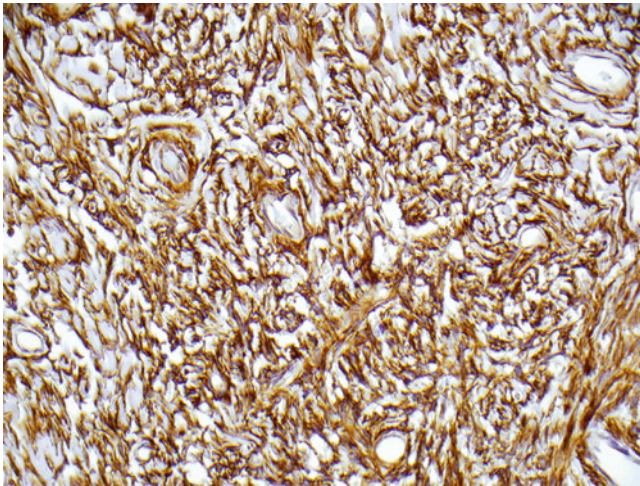


Fig. 29.3 Solitary fibrous tumor shows positive staining for CD34

Table 29.32 Markers for myopericytoma family of tumors (infantile myofibromatosis, solitary myofibroma, infantile hemangiopericytoma, myopericytoma, glomangiopericytoma)

Antibody	Literature
SMA	+
HHF35	+
Calponin	+
h-Caldesmon	- or +
Desmin	- or +
CD34	-

Note: More than half of solid or venous-type angioleiomyomas and rare cavernous type angioleiomyomas are positive for desmin, whereas most of the myopericytomas were negative for desmin. H-caldesmon is typically negative in myofibroma

References: [1–4, 80, 81]

Table 29.33 Markers for glomus tumor

Antibody	Literature
SMA	+
Type IV collagen	+
h-Caldesmon	+
Keratin	-
S100	-
Desmin	-
CD34	-

Figure 29.4

Reference: [82]

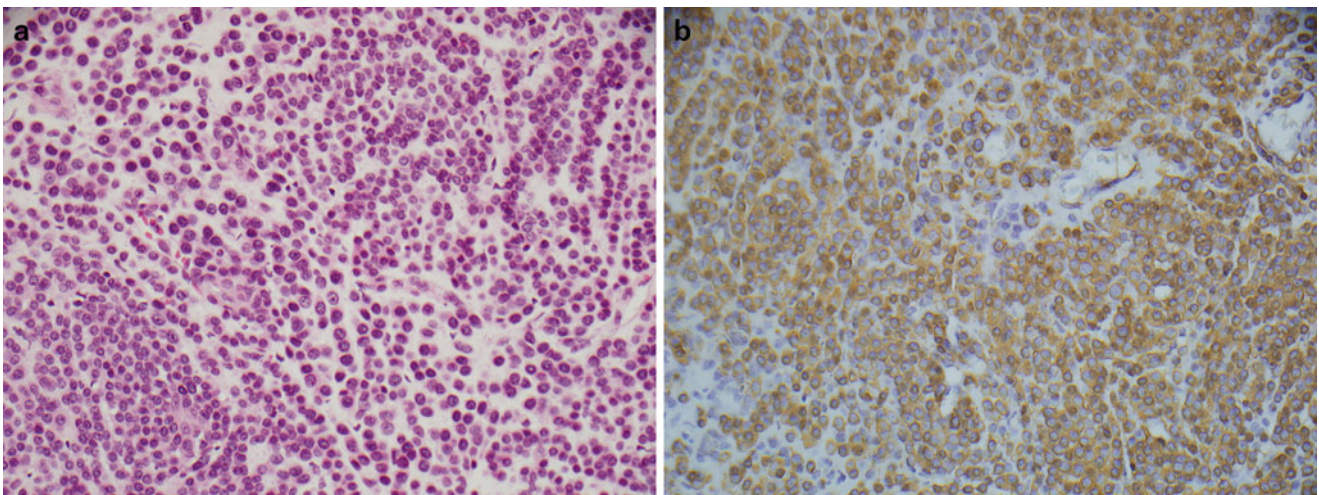


Fig. 29.4 (a) Glomus tumor on H&E section, (b) Glomus tumor shows positive staining for SMA

Vascular Tumors

Table 29.34 Markers for kaposiform hemangioendothelioma

Antibody	Literature
ERG	+
Claudin-5	+
CD31	+
CD34	+
FLI1	+
VEGFR3	+
vWF	–
GLUT1	–
HHV8 LANA	–

References: [83–86]

Table 29.35 Markers for hemangioma

Antibody	Literature
ERG	+
Claudin-5	+
CD31	+
CD34	+
FLI1	+
vWF	+
VEGFR3	+
GLUT1	+ (juvenile type only)
Keratins	– or +

Note: Rare epithelioid hemangiomas are positive for keratins

References: [85, 87, 88]

Table 29.36 Markers for Dabska-type and retiform hemangioendothelioma

Antibody	Literature
ERG	+
Claudin-5	+
CD31	+
CD34	+
FLI1	+
VEGFR3	+
D2-40	+
vWF	+
Keratin	–
EMA	–
S100	–
Desmin	–

References: [85, 89–92]

Table 29.37 Markers for epithelioid hemangioendothelioma

Antibody	Literature
ERG	+
Claudin-5	+
CD31	+
CD34	+
FLI1	+
vWF	+
VEGFR3	+
Keratin	– or +
SMA	– or +
EMA	–

References: [85, 93]

Table 29.38 Markers for angiosarcoma

Antibody	Literature
ERG	+
Claudin-5	+
Vimentin	+
VEGFR3	+ varies
CD31	+
FLI1	+
D2-40	+
Keratins	+ (varies, more often in epithelioid type)
CD34	+ or –
Prox1	+ or –
vWF	– or + (well-differentiated mostly)
EMA	–
S100	–

Note: ERG is a highly sensitive and specific marker for endothelial differentiation

ERG can be positive for prostate carcinoma (50 %), sarcomatoid component of a high-grade urothelial carcinoma, extramedullary myeloid blastic tumors, meningiomas, and rare cases of Ewing sarcoma, AML, undifferentiated large cell carcinoma of lung, and malignant mesothelioma

Claudin-5 can be positive in other non-endothelial tumors, such as carcinomas, biphasic synovial sarcoma, and extraskeletal myxoid chondrosarcoma

Figure 29.5

References: [85, 95–97]

Table 29.39 Markers for Kaposi sarcoma

Antibody	Literature
ERG	+
Claudin-5	+
CD31	+
CD34	+
FLI1	+
vWF	+
HHV8 LANA	+
D2-40	+
VEGFR3	+
vWF	–

Note: HHV8 LANA is a highly sensitive and specific marker for Kaposi sarcoma

References: [85, 98]

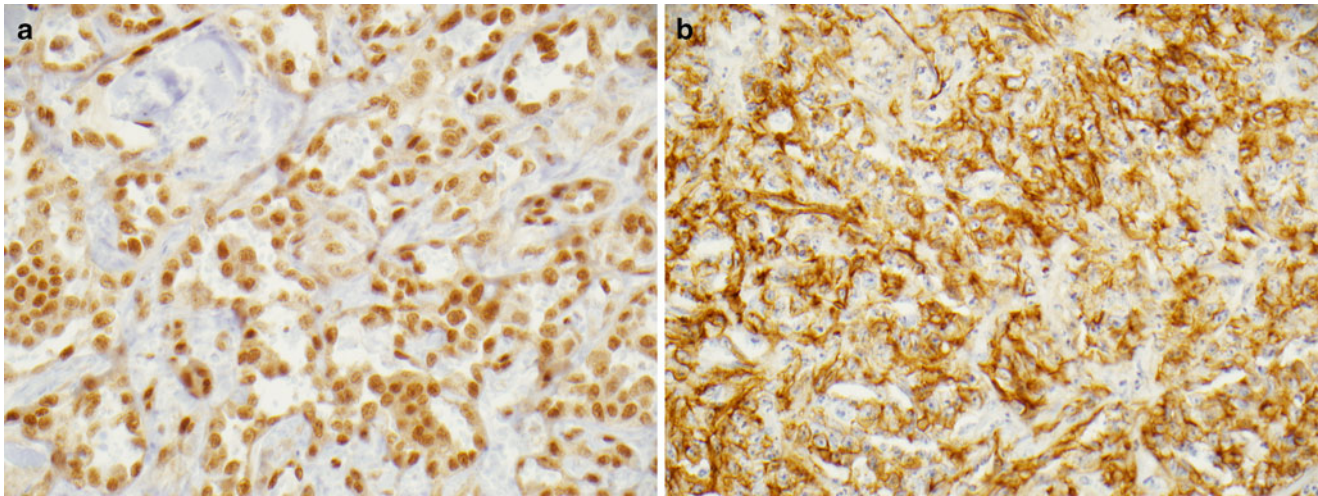


Fig. 29.5 (a) Angiosarcoma shows positive staining for ERG, (b) Angiosarcoma shows positive staining for CD31

Table 29.40 Markers for lymphatic tumors

Antibody	Literature
ERG	+
D2-40	+
Prox1	+
CD31	+
CD34	+
Factor VIII-related antigen	+ or –

Note: Prox1 can be positive for other vascular endothelial tumors, some carcinomas, and rare cases of other sarcomas (Ewing sarcoma, paraganglioma, synovial sarcoma)

References: [95, 99–103]

Nerve Sheath and Neuroectodermal Tumors

Table 29.41 Markers for neurofibroma

Antibody	Literature
S100	+(Schwann cells)
SOX10	+
GAP43	+
CD34	+(fibroblasts)
EMA	+(perineurial cells)
NFP	+(axons)
Calretinin	+

References: [1–4, 104, 105]

Table 29.42 Markers for schwannoma/nerve sheath myxoma

Antibody	Literature
S100	+
SOX10	+
GAP43	+
CD56	+
CD57	+
Calretinin	+
D2-40	+
AE1/AE3	+
EMA	– or +
CD34	–
NFP	–

Note: S100 is not very specific for neural crest differentiation. Except for peripheral nerve sheath tumors, it can express in synovial sarcoma (15 %), Ewing sarcoma/PNENT (21 %), rhabdomyosarcoma (24 %), chondrosarcoma (75 %), and extraskeletal myxoid chondrosarcoma (45 %)

SOX10 is significantly more specific (99 % specificity) than S100 (91 % specificity) for peripheral nerve sheath tumors and more sensitive than S100 for desmoplastic melanoma and clear-cell sarcoma

Cytokeratins are often positive in retroperitoneal or mediastinal schwannoma, but not in peripheral schwannoma. The perineurial cells of the capsule are positive for EMA

Figure 29.6

References: [1–4, 104–106]

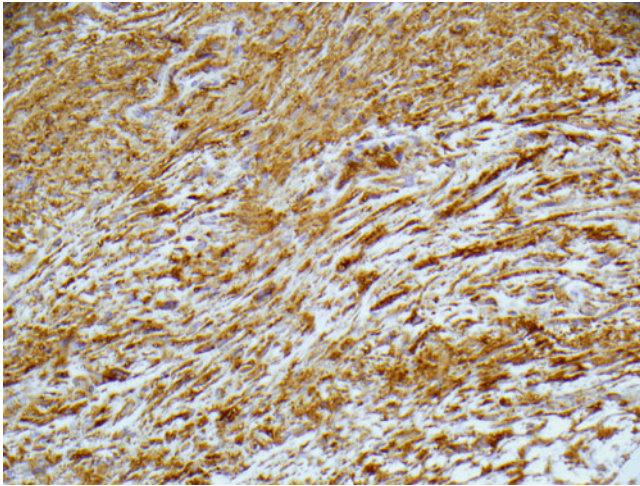


Fig. 29.6 Schwannoma shows positive staining for S100

Table 29.43 Markers for psammomatous melanotic schwannoma/melanotic schwannian tumor

Antibody	Literature
Vimentin	+
Tyrosinase	+
HMB-45	+
Melan-A	+
S100	+
Ki-67 > 5 %	+
PRKAR1A	+ or -
EMA	-
INI1	-
GFAP	-

References: [1–4, 106–109]

Table 29.44 Markers for malignant peripheral nerve sheath tumor (MPNST)

Antibody	Literature
GAP43	+
S100	+ or -
SOX10	+ or -, majority show $\geq 2+$ staining
GFAP	+ or - Focal
CD56	+ or -
CD57	+ or -
INI1	+ or -
MDM2	+ or -
D2-40	- or +
Desmin	- or +
CDK4	- or +
TLE1	- or +
Keratins	-
HMB45	-
MART1	-

Note: S100 is focally positive in spindled MPNSTs and diffusely and strongly positive in epithelioid MPNSTs 50 % of epithelioid MPNSTs show loss of INI1 expression

(continued)

Table 29.44 (continued)

Desmin is positive in some spindle cell MPNST

75 % of epithelioid MPNSTs are positive for D2-40. 21 % of spindle cell MPNSTs are positive for D2-40

GAP43 is more sensitive marker than S100 in MPNSTs. 70 % of desmoplastic melanomas and rare cases of leiomyosarcomas, spindle cell melanoma, synovial sarcoma, and clear cell sarcoma are positive for GAP43, most of them shows focal, faint staining

References: [104, 110–113]

Table 29.45 Markers for granular cell tumor

Antibody	Literature
Vimentin	+
NSE	+
Calretinin	+
S100	+
SOX10	+
CD68	+
Inhibin	+
Protein gene product 9.5 (PGP9.5)	+
CD57	+ or -
CAM5.2	-
EMA	-

Note: Inhibin is only positive in benign granular tumor

S100/NSE are negative in congenital granular cell tumor

References: [105, 114, 115]

Table 29.46 Markers for cellular neurothekeomas (fibrohistiocytic tumor)

Antibody	Literature
Vimentin	+
NKI/C3	+
CD10	+
Protein gene product 9.5	+
CD68	- or +
SMA	- or +
S100	-
GFAP	-
Melan-A	-

References: [116, 117, 174]

Table 29.47 Markers for perineurioma

Antibody	Literature
EMA	+ Weak
Claudin-1	+
GLUT1	+
CD34	+ or –
CD99	+ or –
SMA	– or +
MSA	– or +
GFAP	– or +
AE1/AE3	– or +
CAM5.2	– or +
NFP	–
Desmin	–
S100	–

Note: Most of the tumors show weak staining for EMA

References: [118–120]

Table 29.48 Markers for neuroblastoma

Antibody	Literature
NB84	+
MAP-2	+
Neurofilament	+
Synaptophysin	+
NSE	+
Protein gene product 9.5	+
β -catenin	+
CD56	+
Chromogranin	+ or –
Myogenin	–
Desmin	–
Keratin	–
TdT	–
CD99	–
S100	–

Note: MAP-2 is usually strongly positive for neuroblastoma and negative for other small blue round cell tumors

Figure 29.7

References: [121–124]

Table 29.49 Markers for clear cell sarcoma of soft parts

Antibody	Literature
S100	+
HMB45	+
HMB50	+
Tyrosinase	+
MITF	+
Melan-A	+ or –
SOX10	+ or –
Synaptophysin	– or +
CD56	– or +
EMA	– or +
C-kit	– or +
CD34	– or +
Keratin	– or +
SMA	–
Desmin	–
CAM5.2	–

References: [125, 126]

Tumors of Uncertain Differentiation

Table 29.50 Markers for myxoma

Antibody	Literature
Vimentin	+
SMA	– or +
CD34	– or +
Desmin	– or +
S100	–

References: [1–4]

Table 29.51 Markers for aggressive angiomyxoma

Antibody	Literature
Desmin	+
Vimentin	+
MSA	+
ER	+
PR	+
CD34	+ or –
SMA	– or +
S100	–
Keratin	–

Reference: [32]

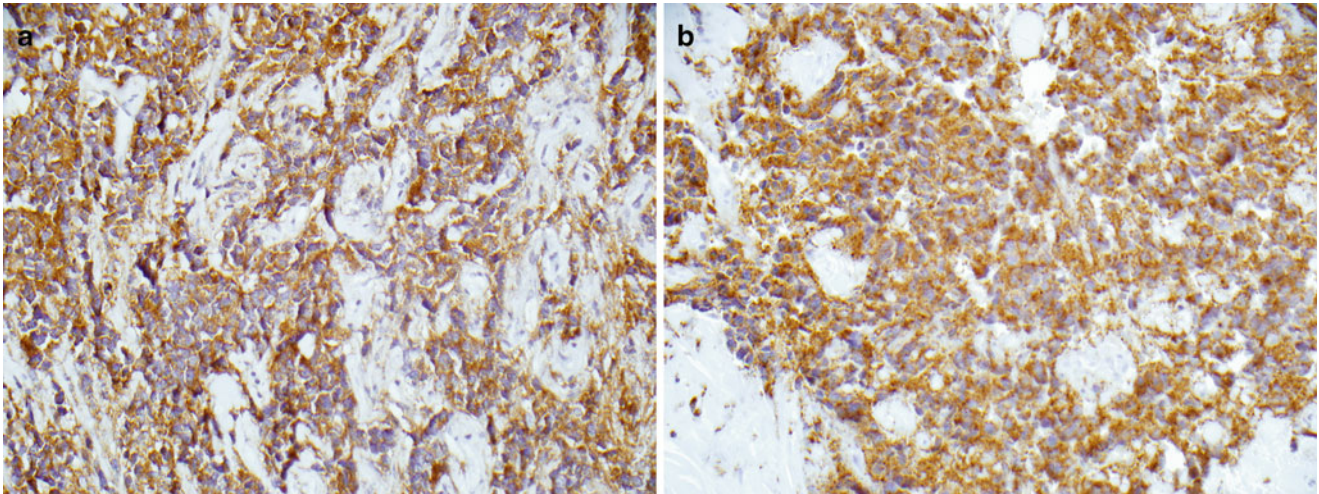


Fig. 29.7 (a) Neuroblastoma shows positive staining for CD56, (b) Neuroblastoma shows positive staining for synaptophysin

Table 29.52 Markers for ossifying fibromyxoid tumor of soft parts

Antibody	Literature
Vimentin	+
S100	+
NF	+
EAAT4	+
INI1	+
CK	- or +
EMA	- or +
SMA	- or +
Desmin	- or +
CD56	- or +
CD57	- or +
MUC-4	- or +
NSE	- or +
GFAP	- or +

Note: S100 is positive in 70 % of typical tumor and 30 % of malignant tumor

74 % of OFMTs show mosaic pattern INI1 expression.
26 % of OFMTs show retained INI1 expression

References: [128–131]

Table 29.53 Markers for mixed tumor/myoepithelioma/parachordoma(myoepithelial tumors)

Antibody	Literature
Vimentin	+
S100	+
AE1/AE3	+ (variable)
Calponin	+
Pan CK	+ or -
Cam5.2	+ or -
EMA	+ or -
CK14	- or +
SMA	- or +
CD57	- or +
NSE	- or +
GFAP	- or +
p63	- or +
Desmin	- or +

References: [132]

Table 29.54 Markers for pleomorphic hyalinizing angiectatic tumor

Antibody	Literature
CD34	+
Vimentin	+
EMA	- or +
S100	-
Desmin	-
Keratin	-
CD31	-

References: [1–4]

Table 29.55 Markers for phosphaturic mesenchymal tumor

Antibody	Literature
FGF23	+
Vimentin	+
CD31	-
CD34	-
S100	-

References: [3, 133]

Table 29.56 Markers for perivascular epithelioid cell family of tumors (PEComas) (angiomyolipoma of the kidney or other organs, clear cell sugar tumor of the lung, lymphangioleiomyomatosis, clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres)

Antibody	Literature
CD1a	+
HMB45	+
HMB50	+
Melan-A	+
MITF	+
NKI/C3	+
Vimentin	+
Calponin	+
MSA	+
SMA	+

(continued)

Table 29.56 (continued)

Antibody	Literature
h-Caldesmon	+
Desmin	+
Tyrosinase	+ or -
S100	- or +
Keratin	- or +
TFE3	- or +
CD34	-
EMA	-
CD117	-

References: [134–136]

Table 29.57 Markers for epithelioid sarcoma

Antibody	Literature
Vimentin	+
AE1/AE3	+
CK8	+
CK19	+
EMA	+
CA125	+
D2-40	+
FLI1	+
CD34	+ or -
p63	- or +

(continued)

Table 29.57 (continued)

Antibody	Literature
ERG	- or +
INI1	- or + (typically lacks nuclear positivity)
MSA	- or +
Desmin	-
S100	-
CK14	-
CK5/6	-
CK20	-
CD31	-
Claudin-5	-
Prox 1	-

Note: More than 90 % of epithelioid sarcomas show loss of INI1 expression

INI1 loss can be seen in renal medullary carcinoma, epithelioid MPNST, myoepithelial carcinomas, extraskeletal myxoid chondrosarcomas, and poorly differentiated chordomas

Many epithelioid sarcomas are positive for ERG by using anti-ERG antibody raised against to the N-terminus of ERG, while only rare cases of epithelioid sarcomas are positive by using anti-ERG antibody raised against to the C-terminus of ERG

Figure 29.8

References: [137–141]

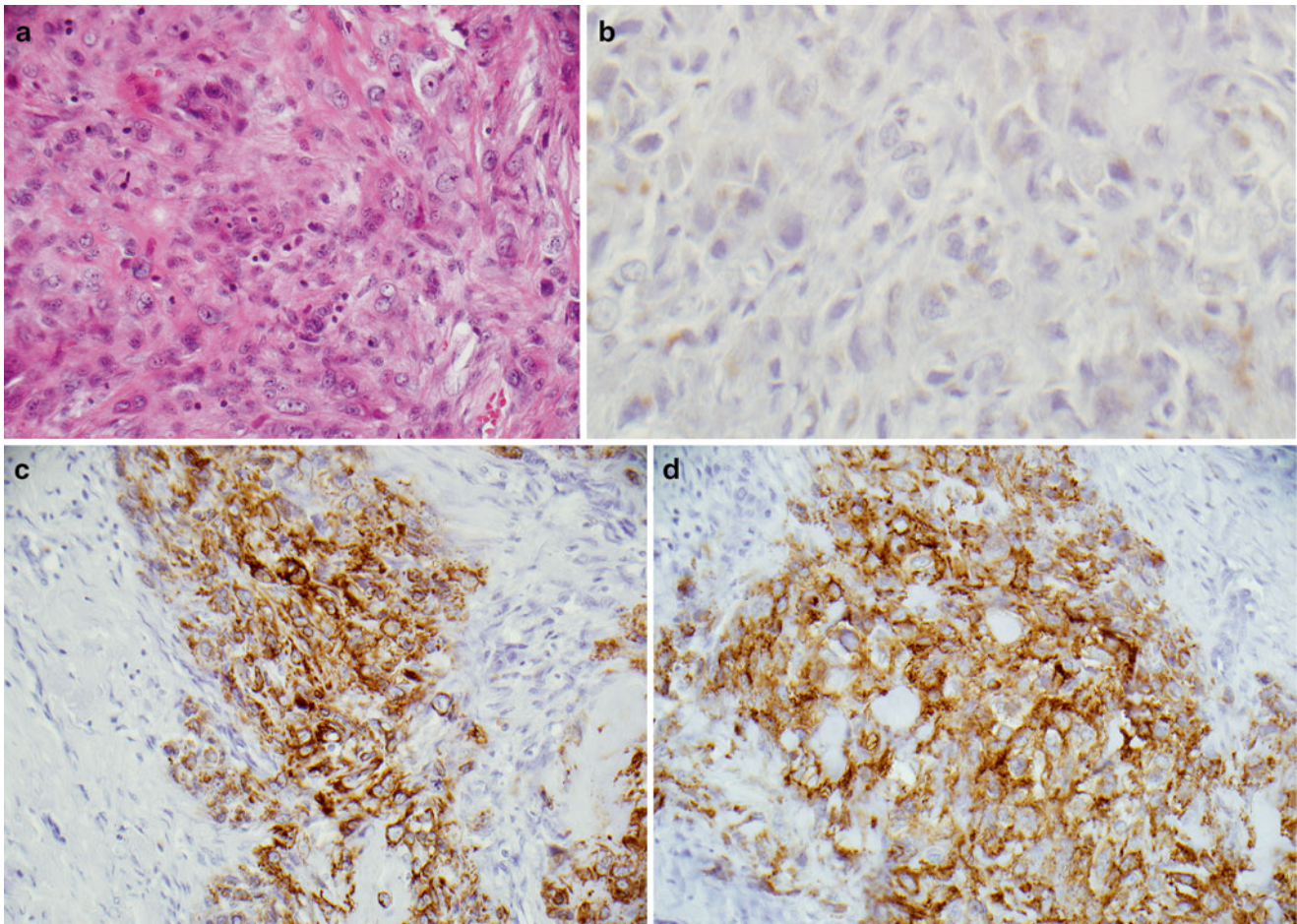


Fig. 29.8 (a) Epithelioid sarcoma on H&E section, (b) Epithelioid sarcoma shows no nuclear staining for INI1, (c) Epithelioid sarcoma shows positive staining for AE1/AE3, (d) Epithelioid sarcoma shows positive staining for EMA

Table 29.58 Markers for alveolar soft part sarcoma

Antibody	Literature
TFE3	+
NSE	– or +
Vimentin	– or +
S100	– or +
NSE	– or +
CD34	– or +
CK	–
EMA	–
Synaptophysin	–
Myogenin	–
Melan-A	–

Note: TFE3 is highly sensitive and specific marker of alveolar soft part tumor. However, Xp11 translocation renal cell carcinoma, granular cell tumor, and a subset of PEComa and epithelioid hemangioendotheliomas can show positivity for TFE3

References: [1, 142–144]

Table 29.59 Markers for Ewing sarcoma and primitive neuroectodermal tumor (ES/PNET)

Antibody	Literature
NKX2.2	+
CD99	+
FLI1	+
Vimentin	+ or –
Synaptophysin	– or +
NSE	– or +
CK	– or +
CD117	– or +
S100	– or +
ERG	– or +
TdT	–
Desmin	–

(continued)

Table 29.59 (continued)

Antibody	Literature
CD45	–
CD56	–
Synaptophysin	–

Note: ES/PNET usually shows a membrane-staining pattern for CD99

Most of Ewing sarcoma/PNET show diffuse staining for NKX2.2. Less than 10 % of non-Ewing sarcomas are positive for NKX2.2, including neuroblastomas, small cell carcinoma, mesenchymal chondrosarcoma, and malignant melanoma

Expression of ERG can identify ERG-rearranged Ewing sarcomas

Figure 29.9

References: [145–147]

Table 29.60 Markers for synovial sarcoma

Antibody	Literature
TLE1	+
EMA	+ Epithelial of biphasic tumors, Focal in monophasic examples
Bcl-2	+
CK7	+
CK19	+
Calponin	+
NY-ESO-1	+
CD99	+
AE1/AE3	+ or –
E-cadherin	+ or –
β-catenin	– or +
S100	– or +
SMA	– or +
CD117	– or +
SOX10	– or +

(continued)

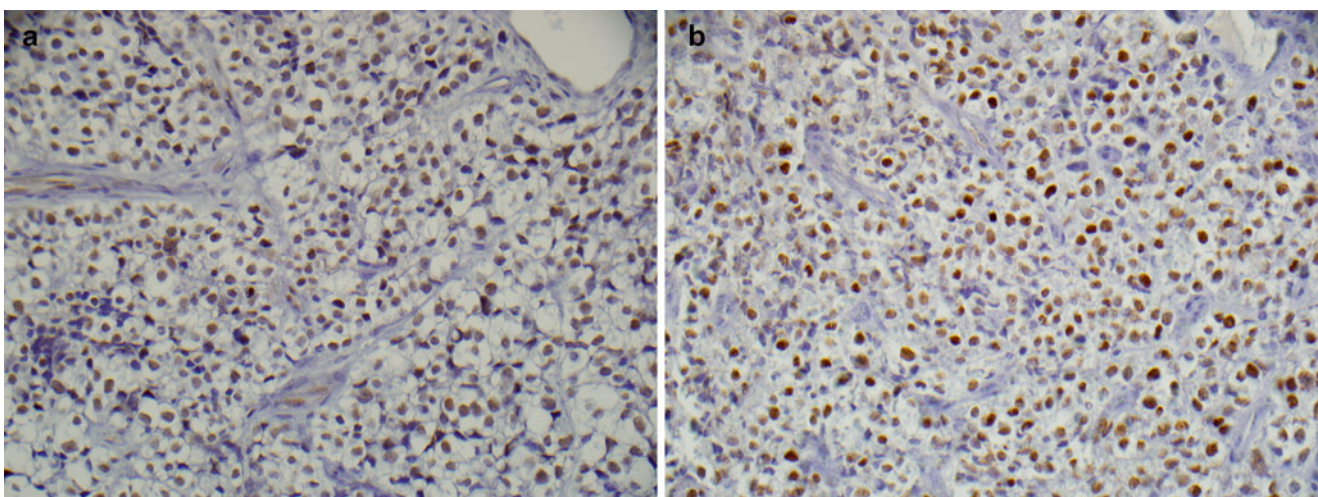


Fig. 29.9 (a) Ewing sarcoma shows positive staining for FLI1, (b) Ewing sarcoma/PNET shows positive staining for NKX2.2

Table 29.60 (continued)

Antibody	Literature
Desmin	–
CD34	–
h-Caldesmon	–

Note: Cytokeratin and EMA expression is strong and diffuse in the glandular component of biphasic synovial sarcoma and focal in monophasic synovial sarcoma and poorly differentiated synovial sarcoma

TLE1 expression is found in almost all synovial sarcomas, but also seen in a subset of acral myxoinflammatory fibroblastic sarcoma, endometrial stromal sarcoma, epithelioid sarcoma, leiomyosarcoma, lipoma, liposarcoma, neurofibroma, rhabdomyosarcoma, schwannoma, solitary fibrous tumor, undifferentiated pleomorphic sarcoma, and MPNST

76 % of synovial sarcomas and rare cases of GIST, MPNST, DFSP, angiosarcoma, mesothelioma, chondrosarcoma, osteosarcoma, dedifferentiated liposarcoma, alveolar soft part sarcoma, and Ewing sarcoma are positive for NY-ESO-1

NY-ESO-1 expression has not been seen in leiomyosarcomas, hemangiopericytoma/solitary fibrous tumors and cellular schwannomas

Monophasic synovial sarcoma can rarely be positive for CD34 (6 %)

Figure 29.10

References: [1–4, 148–155]

Table 29.61 Markers for desmoplastic small round cell tumor

Antibody	Literature
Vimentin	+
Desmin	+
AE1/AE3/CAM5.2/CK-PAN	+
EMA	+
Ber-EP4	+
WT-1	+
MOC31	+
NSE	+ or –
CD15	+ or –
FLI1	+ or –
CD99	– or +
Synaptophysin	– or +
MSA	– or +
SMA	– or +
Calretinin	–
CK5/6	–
CK20	–
Chromogranin	–
Neurofilament	–
S100	–
MyoD1	–
Myogenin	–

Figure 29.11

References: [156–158, 175, 176]

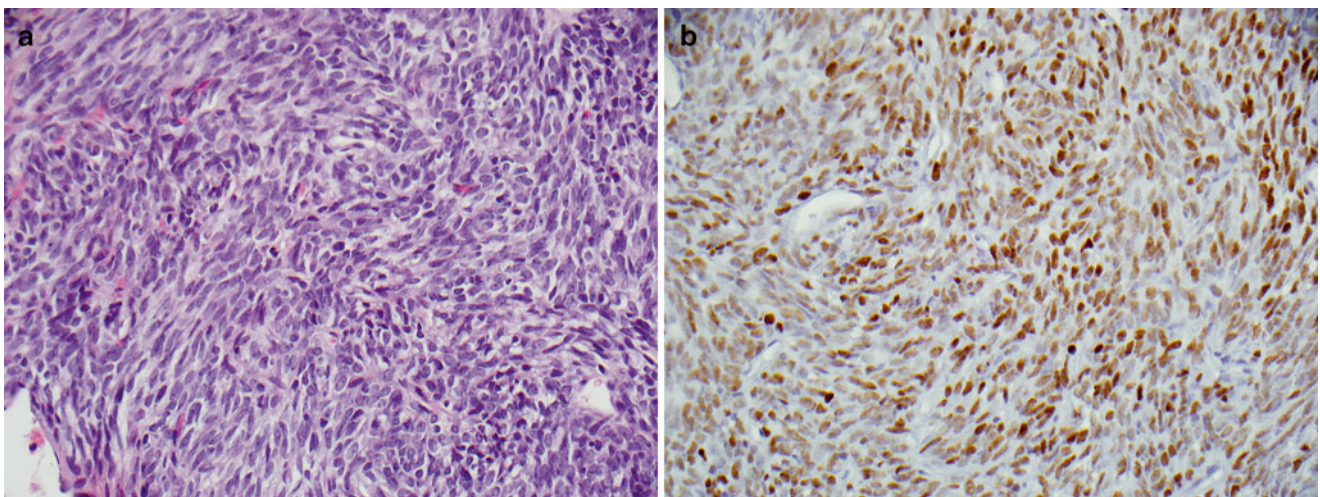


Fig. 29.10 (a) Synovial sarcoma on H&E section, (b) Synovial sarcoma shows positive staining for TLE1

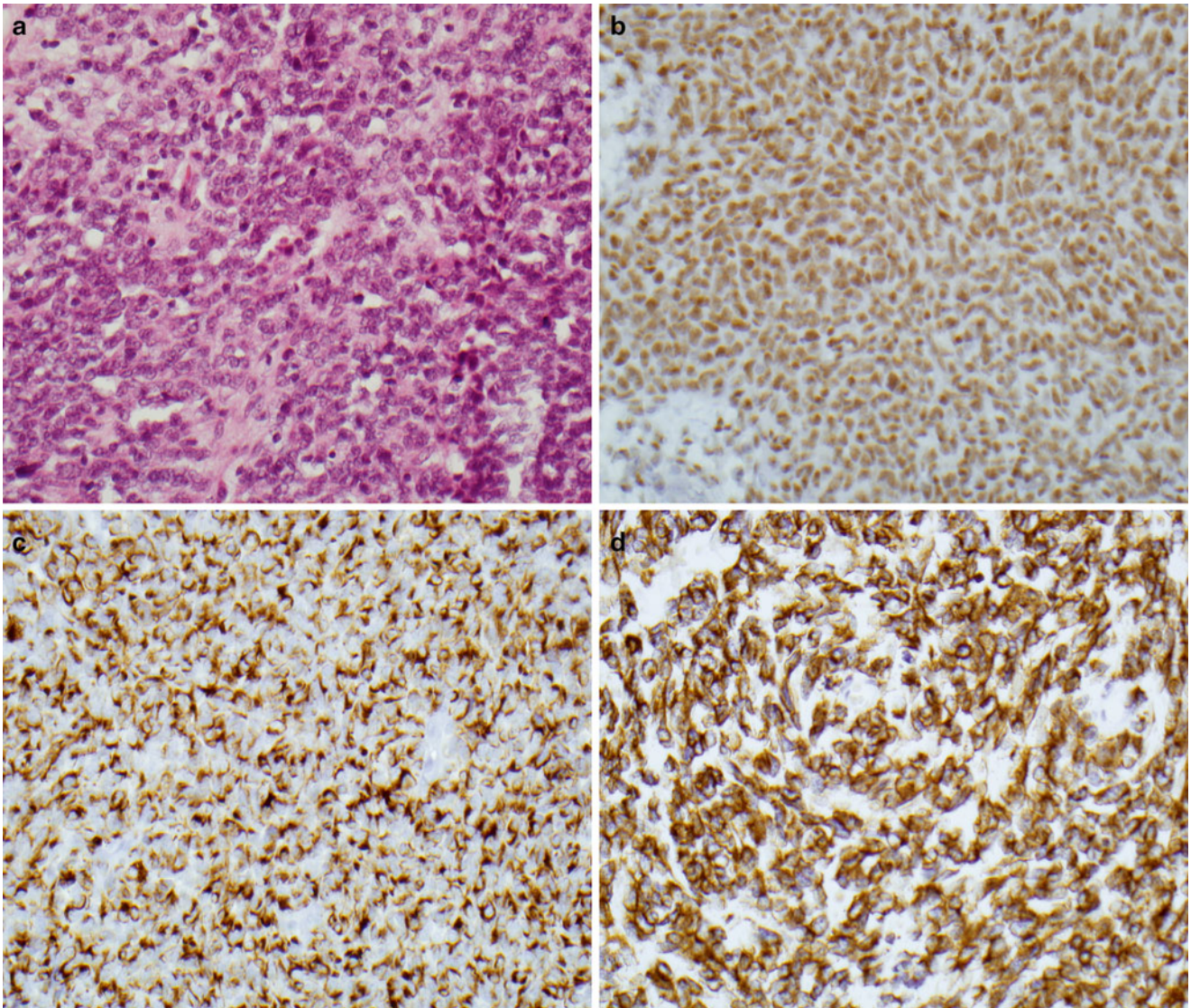


Fig. 29.11 (a) DSRCT on H&E section, (b) DSRCT shows positive staining for WT1, (c) DSRCT shows positive staining for desmin, (d) DSRCT shows positive staining for AE1/AE3

Table 29.62 Markers for malignant extrarenal rhabdoid tumor

Antibodies	Literature
Vimentin	+
CD99	+
Synaptophysin	+ or –
CD57	+ or –
NSE	+ or –
Pancytokeratin	+ or –
CAM5.2	+ or –
EMA	+ or –
S100	– or +
MSA	– or +
SMA	– or +
HMB45	–
Chromogranin	–
Desmin	–
Myoglobin	–
CD34	–
β-catenin	–
GFAP	–
INI1/SMARCB1	–

Note: Loss of INI1 expression is seen in most of malignant extrarenal rhabdoid tumors

References: [1–4, 159, 160]

Bone Tumors

Table 29.63 Markers for mesenchymal chondrosarcoma

Antibody	Literature
SOX9	+
S100	+
Vimentin	+
CD99	+
NSE	+ or –
Desmin	– or +
SMA	– or +
Myogenin	–
AE1/AE3	–
HMB45	–
Myoglobin	–
EMA	–
Synaptophysin	–

Note: S100 is positive in chondrocytes only

CD99 is positive in small cells, negative or focally and weakly positive in cartilaginous areas/

Desmin is usually focally positive in small cells

References: [161–165]

Table 29.64 Markers for chordoma

Antibody	Literature
Vimentin	+
Brachyury	+
CK8	+
CK18	+
CK19	+
EMA	+
CEA	+
S100	+ or –

References: [163, 166, 167]

Table 29.65 Markers for adamantinoma

Antibody	Literature
Vimentin	+
EMA	+
AE1/AE3	+
CK14	+
CK19	+
CK5	+ or –
CK7	– or +
CK13	– or +
CAM5.2	–
S100	–

References: [168–171]

Table 29.66 Markers for Langerhans cell histiocytosis

Antibody	Literature
S100	+
CD1a	+
CD207 (langerin)	+
CD68	+
CD45	–
Keratin	–
EMA	–
CD15	–
CD30	–

References: [172, 173]

Differential Diagnosis

Table 29.67 Inflammatory myofibroblastic tumor (IMT)/inflammatory fibrosarcoma (IF) vs. dendritic reticulum cell tumor (DCT)

Antibody	DCT	IMT/IF
CD21	+	–
CD35	+	–
ALK	–	+ or –
S100	+	–

References: [1–4]

Table 29.68 Inflammatory myofibroblastic tumor (IMT)/inflammatory fibrosarcoma (IF) vs. sarcomatoid urothelial carcinoma (SUC)

Antibody	SUC	IMT/IF
p63	+	-
EMA	+	-
SMA	-	+
ALK	-	+ or -

References: [1-4]

Table 29.69 Myxoinflammatory fibroblastic sarcoma (MFS) vs. Hodgkin's lymphoma (HL)

Antibody	MFS	HL
CD15	-	+
CD30	-	+

References: [1-4]

Table 29.71 Low grade fibromyxoid sarcoma (LGFS) vs. neurofibroma/perineurioma vs. desmoid tumors

Antibody	LGFS	Neurofibroma	Perineurioma	Desmoid tumors
S100	-	+	-	-
EMA	- or +	+	+	-
SMA	-	-	-	+
Desmin	-	-	-	+
MUC4	+	-	-	-

References: [1-4, 40]

Table 29.72 Juvenile xanthogranuloma (JXG)/reticulohistiocytoma (RC) vs. Langerhans cell histiocytosis (LCH)

Antibody	JXG/RC	LCH
CD1a	-	+
S100	-	+
CD68	+	+
CD31	+	-
CD163	+	- or + only in some mononuclear histiocytes

References: [1-4]

Table 29.73 Dermatofibroma protuberans (DFSP) vs. dermatofibroma (DF) vs. fibrosarcoma arising in DFSP

Antibody	CD34	Factor XIIIa
DF	-	+ Larger number of positive cells
DFSP	+	- Smaller number of positive cells
Fibrosarcoma in DFSP	variable	- Smaller number of positive cells

References: [1-4]

Table 29.70 Fibrosarcoma (CF) vs. monomorphic synovial sarcoma (MSS) vs. malignant peripheral nerve sheath tumor (MPNST) vs. spindle cell carcinoma (SCC) vs. spindle cell melanoma (SCM) vs. Dermatofibrosarcoma protuberans (DFSP) vs. spindle cell rhabdomyosarcoma (SCR) vs. leiomyosarcoma (LMS) vs. spindle cell angiosarcoma (SCA)

Antibody	CF	MSS	MPNST	SCC	SCM	DFSP	SCR	LMS	SCA
Desmin	-	-	- or +	-	-	-	+	+	-
Myogenin	-	-	-	-	-	-	+	-	-
SMA	-	- or +	-	-	-	-	-	+	-
EMA	-	+	-	+	-	-	-	-	-
Keratins	-	+	-	+	-	-	-	- or +	-
S100	-	-	+ or -	-	+	-	-	-	-
CD34	-	+ or -	+ or -	-	-	+	-	-	+
Melan-A	-	-	-	-	+	-	-	-	-
TLE1	- or +	+	- or +	-	-	-	-	-	-

References: [1-4, 155]

Table 29.74 Rhabdomyosarcoma (RMS) vs. Ewing sarcoma/PNET (ES/PNET) vs. neuroblastoma (NB) vs. desmoplastic small round cell tumor (DSRCT) vs. synovial sarcoma (SS) vs. lymphoma

Antibody	RMS	ES/PNET	NB	DSRCT	SS	WT	Lymphoma
Myogenin	+	-	-	-	-	-	-
MyoD1	+	-	-	-	-	-	-
Desmin	+	-	-	+	-	+ or -	-
CD99	-	+	-	- or +	- or +	-	-
CD45	-	-	-	-	-	-	+
Keratins	-	- or +	-	+	+	+	-
Synaptophysin	-	+ or -	+	-	-	+	-
Neurofilament	-	-	+	-	-	+	-
WT1	+	-	- or +	+	-	+	- or +

References: [1-4, 175, 176]

Table 29.75 Leiomyoma vs. GIST vs. schwannoma

Antibody	Leiomyoma	GIST	Schwannoma
SMA	+	- or + (variable)	-
Desmin	+	-	-
CD117 (KIT)	-	+	-
DOG-1	-	+	-
CD34	-	+ (variable)	-
S100	-	- or + (especially in intestinal ones)	+

Note: DOG-1 positivity has been shown in some leiomyosarcoma, synovial sarcoma, uterine type retroperitoneal leiomyomas, and peritoneal leiomyomatosis

References: [1-4]

Table 29.76 Glomus tumors (GT) vs. hemangiopericytoma (HPC)/solitary fibrous tumor (SFT) of soft tissue

Antibody	GT	HPC/SFT
SMA	+	-
CD34	-	+
STAT6	-	+

References: [1-4, 79]

Table 29.77 Kaposiform hemangioendothelioma (KH) vs. juvenile capillary hemangioma (CH)

Antibody	KH	CH
CD31	+	+
CD34	+	+
FLI1	+	+
vWF	-	+
GLUT1	-	+

References: [1-4]

Table 29.78 Neurofibroma vs. schwannoma vs. perineurioma

Antibody	Neurofibroma	Schwannoma	Perineurioma
S100	+(schwann cells)	+(all cells)	-
CD34	+(fibroblasts)	- or + capsular and degenerative areas	-
EMA	+(focal)	- or + capsular area	+
NFP	+(highlighting axons)	-	-
Claudin-1	-	-	+
GLUT1	-	-	+

References: [1-4]

Table 29.79 ES/PNET vs. lymphoblastic lymphoma (LL)

Antibody	ES/PNET	LL
CD99	+	+
FLI1	+	+
CD45	-	+
TdT	-	+
CD10	-	+
CD43	-	+

References: [1-4]

Table 29.80 ES/PNET vs. neuroblastoma

Antibody	ES/PNET	neuroblastoma
CD99	+	-
FLI1	+	-
CD56	-	+

References: [1-4]

Table 29.81 Chordoma vs. chondrosarcoma

Antibody	Chordoma	Chondrosarcoma
CK	+	-
EMA	+	-
Brachyury	+	-
S100	+	+
D2-40	-	+

References: [1-4]

Table 29.82 Chordoma vs. renal cell carcinoma

Antibody	Chordoma	Renal cell carcinoma
CK	+	+
EMA	+	+
Brachyury	+	-
S100	+	-
RCC	-	+
CAIX	-	+
KIM1	-	+

References: [1–4]

Table 29.83 Langerhans' cell histiocytosis (LCH) vs. Hodgkin lymphoma (HL)

Antibody	LCH	HL
S100	+	-
CD1a	+	-
CD207	+	-
CD15	-	+
CD30	-	+

References: [1–4]

Table 29.84 Epithelioid sarcoma (ES) vs. epithelioid angiosarcoma (EA) vs. epithelioid malignant peripheral nerve sheath tumor (EPNST) vs. epithelioid leiomyosarcoma (ELMS) vs. sclerosing epithelioid fibrosarcoma (SEF) vs. epithelioid osteosarcoma (EO)

Antibody	ES	EA	EPNST	ELMS	SEF	EO
Vimentin	+	+	+	+	+	+
SMA	- or +	-	-	+	-	-
Desmin	- or +	-	- or +	+	-	-
S100	-	-	+ or -	- or +	-	-
CD31	-	+	-	-	-	-
Keratins	+	- or +	- or +	+	-	-
Osteocalcin	-	-	-	-	-	+
SATB2	nd	-	- or +	- or +	-	+

Note: SATB2 can be focally, weakly positive in rare soft tissue tumors or areas of heterologous osteoblastic differentiation in the soft tissue tumors. More than 85 % colorectal carcinomas are positive for SATB2. Loss of INI1 expression can be seen in epithelioid sarcoma (ES) and epithelioid malignant peripheral nerve sheath tumor (EPNST)

References: [1–4, 177]

Table 29.85 Rhabdomyoma vs. granular cell tumor

Antibody	Rhabdomyoma	Granular cell tumor
CD68	-	+
S100	-	+
MSA	+	-
Desmin	+	-
Myoglobin	+	-

References: [1–4]

Table 29.86 Rhabdomyosarcoma vs. leiomyosarcoma

Antibody	Rhabdomyosarcoma	Leiomyosarcoma
Desmin	+	+
MSA	+	+
Myogenin	+	-
MyoD1	+	-
SMA	-	+
h-Caldesmon	-	+
SMM-H	-	+

References: [1–4]

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