Chapter 14. Potpourri of Quick Morphologic References

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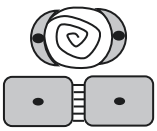
Tumor Differentials 101

Differentials 101: Generic Tumor Types[1]
(Main tumor types seen in ALMOST any organ)

Tumor type	Key features	Key immunostains
Carcinoma	The hallmarks of epithelial cells are cohesiveness (cells stick together), distinct cell borders, and usually abundant cytoplasm (cells resembling this description are called "epithelioid"). Main types of carcinoma are listed below:	Epithelial markers (CK, EMA) +
	Squamous cell carcinoma (SqCC)[2] The two hallmark features are as follows: 1. **Keratinization** – manifesting as keratin pearls/squamous eddies or isolated cells with glassy salmon-pink cytoplasm/dyskeratotic cells: 2. **Intercellular bridges** – desmosomes seen in the prickle cell layer of the epidermis: These two features may not be appreciable in nonkeratinizing or basaloid SqCC 	
	Adenocarcinoma[2] • Easy! All you need is gland (or papillae, micropapillae) formation, however focal. Don't be fooled by neuroendocrine or neuroblastic rosettes though, which can mimic glands. Also, some tumors can become discohesive and mimic true glands (e.g., acantholytic SqCC). • Intracellular mucin is another hint. Detection of mucin may be aided by a mucicarmine stain. 	
	Papillary carcinoma • Papillary carcinomas may be squamous, urothelial, or glandular, depending on the covering epithelium. Fibrovascular cores are a defining feature. • Note that papillary morphology applies to both in situ and invasive lesions (curiously, in situ lesions do not usually invade as papillary carcinomas – e.g., IPMN usually invades as a colloid CA, etc.). • DDx: ovarian serous CA, lung, kidney, thyroid. • Beware – not all that is papillary is a carcinoma (e.g., mesothelioma, myxopapillary ependymoma, papillary meningioma). • **Micropapillary CA** is a variant of papillary CA, which is defined by the absence of fibrovascular cores in the papillae (also typical are clear halos/retraction artifact around micropapillae). DDx includes the ovary (micropapillary serous CA), bladder, breast, lung, and salivary gland. Behavior is typically aggressive. Lymphovascular invasion is nearly universal. 	
Neuroendocrine (NE) neoplasm	This umbrella category encompasses NE neoplasms that are either low grade (e.g., carcinoid) or high grade (e.g., small cell CA, Merkel cell CA). Both types share a set of defining "NE features": • NE cytology: overall nuclear uniformity/monotony (even when high grade), stippled evenly distributed "salt and pepper" chromatin; absence of prominent nucleoli is key (although there are exceptions); low-grade lesions may have scattered cells showing "endocrine atypia," which manifests as large bizarre nuclei with smudged/hyperchromatic chromatin. • NE architecture: nests, trabeculae, ribbons, rosettes (subtle in high-grade lesions).	NE markers (SYN, CHR, CD56, INSM1); CK expression is type-dependent
Small cell carcinoma	Unless otherwise specified, this term implies small cell NE carcinoma, formerly known as "oat cell carcinoma" (note that there are small cell variants of melanoma and some carcinomas). • Despite the name, small size (<3 lymphocytes) is not the only defining feature. • Other key defining features are nuclear molding, very high N/C ratio, lots of mitoses, apoptotic bodies, and geographic necrosis. • Crush artifact with DNA streaming and DNA deposition in vessels ("Azzopardi phenomenon") are characteristic. • NE nature is evidenced by uniform distribution of chromatin (despite high grade), inconspicuous nucleoli, and occasional presence of trabeculae and rosettes.	NE markers (sometimes focal), CK+ (frequently focal), TTF1 often positive (regardless of organ of origin)
Melanoma	• Can look like anything: epithelioid, spindle cell, small cell, pink cell, clear cell, etc. (remember – melanoma is a "great mimicker" in pathology!) • Prominent cherry-red nucleoli and nuclear pseudoinclusions are characteristic. • Presence of melanin pigment is diagnostic, but make sure to distinguish it from hemosiderin and tattoo pigment; also some melanomas are amelanotic.	S100+, SOX10+, Melan-A+, HMB45+, MITF
Lymphoma	• Sheets of cells, ranging from normal lymphocyte-like (e.g., chronic lymphocytic leukemia) to large epithelioid cells (e.g., diffuse large B-cell lymphoma). • Large-cell lymphoma may be histologically indistinguishable from poorly differentiated carcinoma or melanoma. • General signature of lymphomas is cellular discohesion (cells fall apart) and clefted (indented) nuclei. • On high power (especially cytology), look for lymphoglandular bodies (cytoplasmic fragments).	CD45+, many other markers
Sarcoma	• Most commonly composed of spindle or stellate cells but can also look epithelioid, small round blue cell, clear/oncocytic, or highly pleomorphic. • Look for specific features of muscle, vascular, neural, or adipocytic differentiation (see below).	Highly variable, vimentin+ (but not specific)

1. In general, these generic tumors have similar morphology irrespective of the organ of origin, and the origin of metastasis cannot be determined without immunostains or clinical history. However, carcinomas of some organs do have a distinctive morphology. Here are a few notable examples:
   - Colon: tall pseudostratified nuclei and "dirty, garland necrosis"
   - Prostate (acinar type): low-grade and usually monomorphic nuclei with prominent nucleoli forming acini
   - Breast: relatively bland cytology, nests and glands (ductal), or solid sheet/single-file plasmacytoid cells (lobular)
   - Endometrioid: complex cribriform structures with pseudostratified columnar cells (some resemblance to colon), variable squamous differentiation
   - Endocervical: resembles endometrioid with prominent apoptotic bodies and apical mitoses
   - Clear cell RCC: nests of cells with clear or eosinophilic cytoplasm, blood-filled follicles, and complete vascular network surrounding each nest
2. Some tumors can have BOTH glandular and squamous differentiation (known in some organs as adenosquamous CAs); adenoCAs that commonly have a squamous component include pancreatic, endometrioid, lung (this is uncommon in the prostate, colon, breast)

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Differentials 101: Tumors by Cell Type	
Tumor type	*Differential*
Epithelioid tumors	Defined as round, plump cells with some cytoplasm (may be of different quality which generates other patterns as follows) resembling epithelium. DDx includes "carcinoma-melanoma-lymphoma-sarcoma" (the "Big 4"): 1. **Carcinoma**: look for evidence of glandular or squamous differentiation, however focal. Associated CIS/dysplasia seals the deal. 2. **Melanoma**: look for melanin pigment, nuclear pseudoinclusions, and cherry-red nucleoli. Associated melanoma in situ clinches the diagnosis. 3. **Lymphoma**: DLBCL, ALCL, plasmablastic lymphoma, etc. (these can even stain for cytokeratin and ALCL stains for EMA! Always keep these in DDx when encountering a poorly differentiated epithelioid tumor). 4. **Sarcoma**: think of epithelioid sarcoma, epithelioid hemangioendothelioma and angiosarcoma, myoepithelial tumor, epithelioid GIST, and others. **Other**: histiocytic neoplasms, germ cell tumors, epithelioid mesothelioma. Diagnosis usually requires immunostains. Typical initial panel includes CK for carcinoma, SOX10/S100 for melanoma, and CD45 for lymphoma (although some lymphomas may be negative for CD45).
Pink cell tumors (oncocytic/ eosinophilic cytoplasm)	Defined as epithelioid cells with abundant pink cytoplasm. DDx has significant overlap with epithelioid pattern Rhabdoid falls under this category but is specifically coined for cells with dense eosinophilic cytoplasmic inclusions that push the nucleus aside. 1. **Many carcinomas**: most notably HCC (look for bile pigment and lipid vacuoles), RCC (chromophobe or high-grade clear cell, look for nested pattern and prominent vascularity), adrenocortical CAs, thyroid Hurthle cell CA, parathyroid. 2. **Neuroendocrine tumors**: such as paraganglioma and oncocytic carcinoid/NETs 3. **Melanoma**: commonly has abundant pink cytoplasm (always think of melanoma in "pink cell tumor" DDx**.** 4. **Mesenchymal**: ASPS, PEComa, CCS, pleomorphic rhabdomyosarcoma, rhabdoid tumors, epithelioid angiomyolipoma. 5. **Other**: oncocytomas of various organs, granular cell tumor Cytoplasmic granularity in pink cell tumors may be due to the following: • Mitochondria – oncocytic neoplasms of the salivary gland or kidney, Hurthle cell neoplasms of the thyroid • Lysosomes – granular cell tumor • Zymogen granules – acinic cell CA of the salivary gland, acinar cell CA of the pancreas • NE granules – carcinoid tumor
Clear cell (CC) tumors	Defined as epithelioid cells with clear cytoplasm (glycogen, lipid, etc.). Again DDx has significant overlap with epithelioid pattern. First think carcinoma, but certain types of soft tissue tumors (e.g., CCS, PEComa) and very rarely melanoma and lymphoma can be clear. Ironically, many tumors with "clear cell" in their name can be very eosinophilic and have entirely oncocytic pattern rather than clear cell pattern and vice versa. The first-line differential is ccRCC (most common), adrenocortical CA, and ccHCC (uncommon). Complete list of CC neoplasms is vast (almost any carcinoma can have clear cell change, at least focally). Classic examples are: • *Head and neck*: oncocytic and Hurthle cell neoplasms (these are particularly prone to clear cell change), parathyroid, salivary gland neoplasms (e.g., CC carcinoma of salivary gland, myoepithelial tumors, oncocytic tumors, acinic cell, and mucoepidermoid CAs) • *Lung*: CC sugar tumor (PEComa), CC SqCC, or less commonly adenoCA • *GYN tract*: ovarian CC CA • *Soft tissue*: CCS, PEComa
Spindle cell tumors	Defined as cells with a long axis (like a spindle) in contrast to the round appearance of epithelioid cells. Remember: spindle cell melanoma and carcinoma are more common than sarcoma in general! Sarcoma diagnosis always comes after exclusion of carcinoma and melanoma (also mesothelioma in some locations)! Cytologic clues to differentiation in mesenchymal spindle cell neoplasms: • **Smooth muscle**: "cigar"-shaped (blunt-ended) nucleus with bubbly eosinophilic cytoplasm (fascicles intersect at right angles) • **Skeletal muscle**: pink cytoplasmic inclusions with cross-striations and "strap cells" (rhabdomyoblasts) • **Fibroblast/myofibroblast**: bipolar or stellate nucleus with pointy ends and wispy scant lightly eosinophilic cytoplasm myofibroblasts have more plump appearance, small nucleoli, and amphophilic cytoplasm indicating activated state • **Schwannian**: "club-" or "bullet"-shaped nuclei (pointed at one end), typically wavy (look for nuclear palisading) • **Perineurial**: cells are slender and spindled with delicate cytoplasmic processes (storiform pattern) • **GIST (pericyte)**: nucleus is intermediate between smooth muscle (box car) and Schwann cell (pointed). Nuclei can be ridiculously long Other morphologic clues to differentiation are (highly selected examples): • **Vascular**: channels or slit-like spaces with prominent hemorrhage or cytoplasmic vacuoles with RBCs = vascular differentiation (e.g., angiosarcoma or EHE) • **Adipocytic**: presence of lipoblasts. Ironically, some non-adipocytic tumors can have lots of fat (SFT/myofibroblastoma), while some adipocytic tumors (myxoid LPS/dedifferentiated LPS) may not show any fat; lipoblast is only required for diagnosis of pleomorphic LPS
Small round blue cell tumors	Defined as sheets of small round blue cells (duh!). Cells are blue because they have very little cytoplasm. Subtle morphologic hints may be present, but generally diagnosis requires immunostains +/– molecular studies and cytogenetics. DDx is age-dependent (see below).
Tumors with cytoplasmic vacuoles/inclusions	Can be split into several types: • Signet ring cell carcinoma (cytoplasmic mucin vacuole indenting the nucleus): gastric, some lobular breast, urothelial, lung CAs • Rhabdoid tumors (eosinophilic inclusion indenting the nucleus, cells typically discohesive): malignant rhabdoid tumors, carcinomas with rhabdoid component/de-differentiation • Lipoblastic/lipocytic differentiation: lipoblastoma, myxoid liposarcoma, pleomorphic liposarcoma • Intracytoplasmic lumina: vascular tumors such as epithelioid hemangioendothelioma, epithelioid hemangioma, and angiosarcoma may see RBCs in vacuoles, also called "blister" cells • Paranuclear vacuoles: GIST, smooth muscle tumors (bubbly cytoplasm)

Tumor Differentials 101: Tumors by Architectural Pattern (See Glossary in Chapter 16 for definitions)	
Pattern	*Differential diagnosis*
Hemangiopericytoma (HPC)-like pattern (branching staghorn-like vessels)	SFT/hemangiopericytoma (prototype), synovial sarcoma (particularly monophasic), myofibroma/myopericytoma, mesenchymal chondrosarcoma, nasal glomangiopericytoma, nasopharyngeal angiofibroma, MPNST, endometrial stromal sarcoma; may be seen in many other soft tissue lesions (not very specific)
Storiform pattern (cartwheel-like arrangement of cells)	DFSP (prototype), dermatofibroma, perineurioma, some undifferentiated pleomorphic sarcomas
Whorling pattern (concentric growth of tumor cells)	Meningioma (prototype), follicular dendritic cell sarcoma, rarely seen in angiomatoid fibrous histiocytoma, dedifferentiated liposarcoma, and inflammatory myofibroblastic tumor
Nested pattern (packets of cells with intervening stroma)	Neuroendocrine tumors such as pheochromocytoma/paraganglioma (prototype; nested pattern referred to as Zellballen in this setting), ccRCC, urothelial CA, melanoma, PEComa, CCS, and others
Alveolar pattern (nests with central discohesion)	ASPS and alveolar rhabdomyosarcoma (prototypes), nested neoplasms may appear alveolar (e.g., RCC)
Herringbone pattern (fascicles alternating at acute angles)	Fibrosarcoma (infantile or adult type), fibrosarcomatous transformation of DFSP, MPNST, synovial sarcoma, biphenotypic sinonasal sarcoma, spindle cell rhabdomyosarcoma, spindle cell pattern of adamantinoma (rare)
Basaloid tumors (resembling basal cell carcinoma)	Basal cell CA (prototype), basaloid SqCC, HPV-related SqCC, adnexal tumors, adenoid cystic CA, and others
Nuclear palisading in spindle cell tumors	Schwannoma (prototype), smooth muscle tumors, GIST
Biphasic tumors (epithelial and stromal components)	Malignant (both components): sarcomatoid CAs/carcinosarcomas (including the bladder, lung, uterus, etc. – any epithelial organ), biphasic synovial sarcoma, biphasic malignant mesothelioma, pulmonary blastoma, biphasic Wilms tumor, and others Malignant (stroma): malignant phyllodes tumor, Müllerian adenosarcoma Benign: fibroadenoma (breast), adenofibroma/adenomyoma (GYN tract), cystic neoplasms with ovarian-type stroma (mucinous cystic neoplasm of the pancreas, mixed epithelial stromal tumor of the kidney, and others) – stromal cells are ER+, benign mixed tumor (skin/soft tissue), or pleomorphic adenoma (salivary gland)

Abbreviations: *ALCL* anaplastic large-cell lymphoma, *ASPS* alveolar soft part sarcoma, *CCS* clear cell sarcoma of soft tissue, *DFSP* dermatofibrosarcoma protuberans, *DLBCL* diffuse large B-cell lymphoma, *EHE* epithelioid hemangioendothelioma, *GIST* gastrointestinal stromal tumor, *LPS* liposarcoma, *MCC* Merkel cell carcinoma, *MPNST* malignant peripheral nerve sheath tumor, *SFT* solitary fibrous tumor

Potpourri of Differentials	
Tumors with prominent lymphocytes	Carcinoma associated with microsatellite instability (GI, endometrial), seminoma, lymphoepithelioma (LE) and LE-like carcinomas, thymoma, inflammatory myofibroblastic tumor, follicular dendritic cell sarcoma, clear cell CA of ovary, HPV+ oropharyngeal CA
Tumors with prominent neutrophils	Hodgkin lymphoma, neutrophil-rich anaplastic large-cell lymphoma, inflammatory leiomyosarcoma, anaplastic CA of the thyroid, anaplastic CA of the pancreas and lung, sarcomatoid renal cell CA, medullary CA of the kidney, NUT carcinoma
Tumors with prominent eosinophils	Hodgkin lymphoma, Langerhans cell histiocytosis, mast cell tumors, myeloid sarcoma (chloroma), glassy cell carcinoma of the cervix, thyroid sclerosing mucoepidermoid CA with eosinophilia, epithelioid hemangioma (i.e., angiolymphoid hyperplasia with eosinophilia)
Tumors with prominent mast cells	Very non-specific but can be seen in synovial sarcoma, neurofibroma, spindle cell lipoma, myxoid liposarcoma, hemangiopericytoma, hairy cell leukemia (particularly in bone marrow), and others (anything myxoid often has accompanying mast cells)
Tumors with extravasated erythrocytes	Kaposi sarcoma, angiosarcoma, nodular fasciitis, inflammatory myofibroblastic tumor, sinonasal glomangiopericytoma
Tumors associated with granulomas	Classic associations – seminoma, Hodgkin lymphoma, lymphomatoid granulomatosis, Lennert lymphoma, also some carcinomas (e.g., reaction to keratin in SqCC or endometrioid CA with squamous differentiation)
Intranuclear pseudoinclusions	Papillary thyroid CA, hyalinizing trabecular tumor of thyroid, medullary thyroid CA (50%), melanoma, meningioma, pheochromocytoma, lung adenoCA, usual ductal hyperplasia, and others
Hyaline globules	Non-specific but classic associations are yolk sac tumor, Kaposi sarcoma, solid-pseudopapillary tumor of the pancreas, HCC, clear cell CA of GYN tract
Psammoma bodies	Any papillary carcinoma (papillary thyroid CA, serous ovarian CA, papillary CA of the lung, papillary RCC), metanephric adenoma, meningioma (and normal meninges), mesothelioma (and benign mesothelial proliferations in peritoneum), duodenal somatostatinoma
Tumors with melanin pigment	Melanoma (#1, 2, and 3 in the differential), clear cell sarcoma of soft tissue (melanoma of soft parts), Bednar tumor (pigmented dermatofibrosarcoma protuberans; produced by intermixed dendritic cells, not tumor cells). Other neural crest-derived tumors occasionally produce melanin (e.g., melanotic schwannoma, melanotic medulloblastoma)
Mucinous and myxoid tumors	Mucin production is a common feature of carcinomas and soft tissue tumors. Soft tissue mucins are referred to as "myxoid material" to distinguish them from biochemically distinct epithelial mucin. Mucin production is vanishingly rare in melanoma and lymphoma. Colloid CA refers to tumors composed of mainly mucin with only few scattered tumor cells (usually as rows lining colloid at the periphery and floating in mucin as small, inconspicuous clusters). **Common sites of mucinous CA**: the bowel, appendix, ovary, pancreas, lung, breast. Colloid CAs generally considered clinically indolent (except the colon and ovary, mixed data on the lung) **DDx of myxoid soft tissue and bone tumors**: almost ANY soft tissue tumor can be myxoid, at least focally. Major players are intramuscular myxoma, myxofibrosarcoma, myxoid liposarcoma, low-grade fibromyxoid sarcoma, extraskeletal myxoid chondrosarcoma, neurofibroma (myxoid change common), spindle cell lipoma, nodular fasciitis and abdominal fibromatosis (sometimes myxoid), chondromyxoid fibroma, chordoma **Other tumors that may have myxoid change**: malignant mesothelioma, pleomorphic adenoma, myxopapillary ependymoma (filum terminale)
Tumors with squamoid morules (have nuclear β-catenin staining)	Endometrioid CA (low grade), craniopharyngioma (adamantinomatous type), cribriform-morular variant of papillary thyroid CA, pancreatoblastoma, pulmonary blastoma/well-differentiated fetal adenoCA of the lung, basal cell adenoma/adenoCA of salivary glands

Benign Mimics of Malignancy 101 – Watch Out!	
Pleomorphic tumors that are actually NOT high grade (degenerative-type atypia)	Classically, endocrine and NE neoplasms ("NE atypia"), schwannomas ("ancient change"), renal oncocytoma, pleomorphic xantroastrocytoma (PXA), atypical fibroxanthoma (AFX), uterine leiomyomas ("symplastic" change), pleomorphic hyalinizing angiectatic tumor (PHAT). A clue to degenerative nature of atypia is smudgy chromatin and absence of atypical mitoses.
Benign proliferations which may have perineural invasion	Breast sclerosing adenosis, endometriosis, vasitis nodosa, Leydig cell tumors and normal Leydig cells, prostate "benign perineural involvement" (tumor apposed but not surrounding a nerve), pyloric gland metaplasia in the gallbladder, pancreatic islet cells, granular cell tumor
Benign tumors which may have isolated vascular invasion	Pleomorphic adenoma [1, 2], pheochromocytoma/paraganglioma, granular cell tumor [3], giant cell tumor of bone, giant cell tumor of tendon sheath, renal oncocytoma [4]
Benign tumors which may invade the bone (bone invasion ≠ malignancy)	Meningioma, pituitary adenoma, inverted Schneiderian papilloma (extension into the bone occurs as a result of pressure erosion and by itself is not an indication of malignancy)
Benign inclusions in lymph nodes	Müllerian (endometriosis, endosalpingiosis, endocervicosis), nevus (intracapsular location), salivary gland, thyroid (somewhat controversial), mesothelial, breast (heterotopic tissue or benign mechanical transport due to procedure or massage; usually from papillary lesions), renal tubules in patients with large Wilms tumor, lymphangioleiomyomatosis
Benign tumors that can metastasize (!)	Pleomorphic adenoma, uterine benign metastasizing leiomyoma, ameloblastoma, benign fibrous histiocytoma, chondroblastoma, giant cell tumor of the bone, meningioma, pulmonary sclerosing pneumocytoma (formerly sclerosing hemangioma) [5]

Differentials 101: Small Round Blue Cell Tumors (SRBCT)					
Diagnosis	*Age/clinical*	*Location*	*Histologic clues*	*Key immunostains*	*Cytogenetics*
SRBCTs of Adults					
Lymphoma	Any age (type-dependent)	Lymph nodes and any extra-nodal site	No molding (cells are discohesive)	CD45+, CD20 (B cell) or CD3 (T cell), other	Various translocations
Small cell NE carcinoma	Older adults, ectopic hormones, early mets	Any organ	Molding, no nucleoli, "salt and pepper" chromatin, prominent necrosis NE architecture: rosettes, trabeculae (usually subtle)	CK+, NE markers+, TTF-1+ (lung and some non-lung), Neurofilament–, CK20– (opposite to MCC)	
Merkel cell carcinoma (MCC)	60–70 yo	Dermis Head and extremities	Molding, "dusty" vesicular chromatin Rosettes and trabeculae (occasionally)	CK+, NE markers+, always TTF-1–, neurofilament+, CK20+ (punctate), Merkel cell polyomavirus antigen+	
SRBCTs of Young Adults (and Some Children)					
Desmoplastic small round cell tumor (DSRCT)	Mean age 21, M:F = 4:1; rare tumor	Serosal cavities (peritoneum, pleura)	Angulated nests of SRBCs in desmoplastic stroma	WT1+ (C-terminus antibody), CK+, EMA+, NSE+, desmin+/actin–	t(11;22) *EWSR1-WT1*
Synovial sarcoma, poorly differentiated	Any age, typically young adults; mean age 26; 20% <20 yo	Most commonly extremities but can occur almost in any site	High-grade SRBCT, distinction from Ewing sarcoma or other round cell sarcoma usually requires cytogenetics or molecular study	TLE1+, CK/EMA–/+ (patchy at best), poorly-differentiated cases usually CD99+	t(X;18) *SS18- SSX1/2* A small subset can be *SS18* FISH negative but would be positive by other methods such as RT-PCR
Olfactory neuroblastoma (esthesioneuroblastoma)	Bimodal peaks: ages 15 and 55	Roof of nasal fossa (cribriform plate)	Similar to abdominal neuroblastoma: fibrillar rosettes and fibrillar stroma (neuropil), ganglion cells generally absent	NE markers+ (SYN most sensitive), CK can be focal but EMA always –, sustentacular cells S100+, calretinin+	
Small cell osteosarcoma	Bimodal age peaks: 20s and 50s	Around knee (distal femur, proximal tibia)	Tumor osteoid required for diagnosis	SATB2+	
Mesenchymal chondrosarcoma	Typical range 10–40yo (peak 20s and 30s)	Axial skeleton, also in soft tissue	Difficult to recognize if chondroid area is not present	SOX9+ (non-specific), S100+ in chondrocytes	*HEY1-NCOA2*
High-grade myxoid (round cell) liposarcoma	Peak incidence in the 30s	Deep soft tissue of extremities (thigh)	Subtle chicken-wire vessels; variable number of lipoblasts (not required for diagnosis but helpful in recognition)	S100+ in adipocytes (immunostains not helpful for the diagnosis; diagnosis requires cytogenetic or molecular tests)	t(12;16) or t(12;22) *FUS* (or *EWSR1*)-*DDIT3*

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SRBCTs of Children (and Some Adults) – 2[1]					
Diagnosis	*Age/clinical*	*Location*	*Histologic clues*	*Key immunostains*	*Cytogenetics*
Lymphoblastic lymphoma (LBL) (>80% are T cells)	Peaks in adolescence, rare in adults Boys>>girls #1 pediatric malignancy (together with leukemia)	Thymus (>50%), nodes, spleen, and others	Dense medium-size lymphocytes, blastic ("fine lacey") chromatin, inconspicuous nucleoli No molding (cells are discohesive) Many mitoses, sometimes "starry sky" pattern (similar to Burkitt lymphoma)	CD45 variable, TdT+, CD34+ CD3+ (if T cell) frequently CD99+	Various translocations
Myeloid sarcoma (leukemic infiltrate outside of marrow, aka chloroma)	Wide age range, may be de novo or have history or concurrent leukemia or myeloid disorders	Skin, lymph nodes, and bone but many more organs can be involved	Diffuse, monotonous mononuclear cells that often infiltrate background structures; cells have blastic chromatin with variable nucleoli and scant cytoplasm	CD43+, myeloperoxidase+, lysozyme+, can be CD99 + (pitfall)	Various translocations
Neuroblastoma	Peak age 2 yrs, 90% by age 8, rare in young adults #1 solid extracranial malignancy and #3 overall malignancy (after leukemia/lymphoma and CNS) in kids	Adrenal medulla, sympathetic ganglia	Fibrillar stroma (neuropil) and fibrillar (Homer Wright) rosettes Ganglion cells and Schwannian stroma in better differentiated tumors No molding (cells are evenly spaced apart)	NE markers+, PHOX2B (new marker)	Poor prognosis: N-*myc* amplification, -1p, +17q Good prognosis: age < 1 year, hyperdiploidy
Ewing sarcoma (ES)/PNET (primitive neuroectodermal tumor)[2]	Mean age 11–15 yo, but can occur at any age; rare in ages <5 and > 30 Presents as rapidly growing painful mass. Skeletal form clinically mimics osteomyelitis.	(1) Skeletal: lower extremities and pelvis (2) Soft tissue: paravertebral, extremities, retroperitoneum	Monomorphic uniform cells Vesicular (open) chromatin +/– Homer Wright rosettes Cytoplasmic vacuoles (glycogen/PAS+) No neuropil outside rosettes and no ganglion cells (unlike neuroblastoma)	CD99+, NKX2.2+, NE markers +/–, some may be + for ERG (do not confuse for vascular lesion)	t(11;22) *EWSR1-FLI1* – 90% t(21;22) *EWSR1-ERG* 5% Many more rare fusions
***CIC*-rearranged sarcoma**	Mean age, 24; range 6–62	Trunk and extremities, viscera, rarely the bone	Cytology slightly more atypical than ES. Most have geographic necrosis; some have myxoid changes or spindling of cells	ETV4+ (negative in other SRBCTs), WT1+, variable CD99 (diffuse in only 20% of cases in contrast to ES)	t(4;19) or t(10;19) *CIC-DUX4*
***BCOR*-rearranged sarcoma**	Mean age 15; range 2–44 M>>F Reference: [6]	Bone>>soft tissue>viscera	Round and spindle cells. Resembles poorly different synovial sarcoma	BCOR+, CCNB3+, SATB2+, Cyclin D1+, TLE1+	inv(X) *BCOR-CCNB3* t(X;4) *BCOR-MAML3*
Alveolar rhabdomyosarcoma, solid variant	Peak age 9, can occur up to age 30 (older than embryonal) #1 pediatric sarcoma	Deep muscles of extremities; trunk (distinct from embryonal)	Look for hints of myogenic differentiation: pink cytoplasmic inclusions (cross-striations are rarely evident) and multinucleated wreath-like giant cells Dense chromatin (unlike ES) Cells are discohesive	Desmin+ (can highlight cross-striations), MyoD+, myogenin+ (usually diffuse)	t(2;13) *PAX3- FOXO1* t(1;13) *PAX7- FOXO1*
Wilms tumor (nephroblastoma), blastema predominant	Peak age, 3.5 yo; range 3 mo–6 yrs.; always >3 mo and <16 yrs. of age #1 pediatric renal tumor	Kidney	May see areas with classic triphasic histology Molding present (unlike lymphoma, neuroblastoma) [7]	WT1+	11p13 (*WT1* gene) deletion/mutation, Trisomy 12
Medulloblastoma	Peak age 7 yo; usually <20 yo (70% under age 16)	Cerebellum	High-grade SRBCT Homer Wright rosettes Sometimes nodular architecture	SYN+	Isochromosome 17q
Retinoblastoma	Young children	Retina	Flexner-Wintersteiner rosettes	CRX/OTX3 (new marker)	13q14 (*RB* gene) deletion/mutation
Hepatoblastoma, small-cell variant	90% in kids under age 5	Liver	Diagnosis requires areas of better-differentiated hepatoblastoma		

1. DDx also includes small cell osteosarcoma and mesenchymal chondrosarcoma (see SRBCTs of Young Adults). Note that not all "blastomas" are pediatric small round cell tumors: for example, pulmonary blastoma and hemangioblastoma are tumors of adulthood that are non-SRBCT.

2. Ewing sarcoma (ES) and PNET (peripheral primitive neuroectodermal tumor) are now regarded as morphological manifestations of one tumor type; both are characterized by t(11;22) translocation. In general, there are usually more neuroendocrine features in PNET, whereas ES is thought to be a more undifferentiated tumor. However, there is a considerable overlap in clinical presentation, morphology, and prognosis, and most pathologists no longer separate them. In fact, the term PNET was retired in the most recent soft tissue WHO.

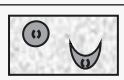
General comment: While not entirely specific (like most stains or morphologic features), many of the soft tissue sarcomas that are associated with specific molecular abnormalities have a distinct cytologic monotony that can serve as a subtle tip. Rare exceptions do occur: some translocation-associated tumors can be pleomorphic (such as myxoinflammatory fibroblastic sarcoma); rarely synovial sarcoma or Ewing sarcoma may show more pleomorphism if they harbor *TP53* mutations.

Abbreviations: *SRBCT* small round blue cell tumor

There's a Fungus Among Us! Quick Reference for Histologic Identification of Fungi

Fungi are encountered in two major settings: (1) surface dwellers and colonizers (e.g., mucocutaneous candidiasis and fungus ball, respectively) and (2) infections involving visceral organs/soft tissue. The latter category includes two types of fungi: (1) **opportunistic** (occurring in immunocompromised host) vs. **pathogenic** (able to infect immunocompetent host). Classic opportunistic fungi include *Pneumocystis* and *Zygomycetes*. Classic pathogenic fungi include dimorphic fungi, which exist as molds in nature and yeast in tissue: *Histoplasma* (*Histo*), *Blastomyces* (*Blasto*), *Coccidioides* (*Cocci*), and *Paracoccidioides*. *Cryptococcus* (*Crypto*) is predominantly opportunistic. When you encounter a fungus in visceral organs, your DDx should vary according to the patient's immune status.

Fungi are generally inconspicuous in H&E sections and are best visualized by "pan-fungal" stains – GMS and PAS – although some larger fungi (*Blasto*, *Cocci*, *Zygomycetes*) are readily visible in H&E. *Crypto* can also be at least suspected on H&E. The sizes of a RBC and a lymphocyte nucleus are ~7 μm; these may be used as a handy-size reference. The most common histologic response to fungi is granulomatous inflammation, but some may manifest with other features, such as granulomas with neutrophils (*Blasto*), granulomas with eosinophils (*Cocci*), or frothy intra-alveolar exudate (*Pneumocystis*).

Organism or disease	Appearance (GMS or PAS)	Organism – key features	Typical tissue reaction	Comment
Budding Yeast in Tissue				
Histoplasma capsulatum	 "tiny critters in a macrophage (MF) and in tissue"	– 2–5 μm – Narrow-based "teardrop" budding (difficult to see in tissue) – Pseudocapsule (faint halo due to retraction artifact) on Giemsa – no true capsule – Mostly oval shapes – Predominantly intracellular but usually spill into surrounding tissue, where organisms tend to remain in clusters – DDx: *Crypto*, *Pneumocystis*, *Candida*, *Penicillium* (rare), and small intracellular protozoa (*Leishmania*)	– Granulomas with fibrocaseous "infarct-like" necrosis – Old lesions typically hyalinize/calcify	– Ohio-Mississippi river valley – Carrier: birds and bats ("cave fever") – Sites: lung, GI, disseminated – Organisms can stain extremely pale with GMS – look closely!
Cryptococcus neoformans	 "soap bubbles"	– 2–15 μm – Narrow-based budding – Highly variable size (unlike *Histo* or *Blasto*, which are uniform) – Variable shape: spherical and elongated (football-shaped) forms – Polysaccharide capsule (mucicarmine+, PAS+, alcian blue+), but some organisms are capsule-deficient. India ink + (historic use only) – Cell wall contains melanin pigment (Fontana-Masson+; pigment not apparent on H&E). Note that positive melanin stain is not entirely specific for *Crypto* since *Cocci*, *Blasto*, and *Sporothrix* can also be positive	– Granulomatous inflammation (+/– necrosis) – Histiocytes with bubbly cytoplasm (where organisms are usually visible by H&E)	– Carrier: pigeons (droppings) – Sites: meningitis, the lung, other deep infections
Blastomyces dermatitidis	 "snowman"	– 8–15 μm – Broad-based budding – Thick double walls ("double contour"), multinucleation – Cell walls can be weakly positive for mucin stains	– Granulomas with neutrophils	– Ohio-Mississippi river valley – Sites: lung, skin, bone, disseminated
Paracoccidioides brasiliensis (aka South American blastomycosis)	 "mariner's wheel"	– 5–30 μm (wide size variation is characteristic) – Large spherule with multiple peripheral narrow-based buds (although diagnostic, the multiple budding cells are usually inconspicuous)		– Africa, Central and South America – Sites: skin, bone, mucous membranes (mimics *Blasto*)
Sporothrix schenckii	 "cigar bodies"	– 2–6 μm – Round or elongated "cigar-shaped" budding yeast, usually rare and difficult to find in tissue – "Asteroid bodies" (Splendore-Hoeppli phenomenon) – crystalline structures representing antigen-antibody complexes. Classic for *Sporo* but not specific		– "Rose-gardener's disease" – Sites: SubQ
Non-budding Spherical Fungi in Tissue				
Coccidioides immitis	 "bag of marbles"	– Thick-walled spherule (50–200 μm) packed with endospores (2–5 μm) – Endospores frequently spill into the surrounding tissue and may resemble *Histoplasma* (but there is no budding) – **DDx:** • *Rhinosporidium*: nasal fungus, much larger than *Cocci*. GMS+ • Myospherulosis: surgical packing material with entrapped RBCs in the nose/sinus. GMS–, PAS–, hemoglobin+	– Granulomas with eosinophils	– Southwest American deserts ("valley fever") – Sites: lung, skin, disseminated
Penicillium marneffei	 "tiny critters in a MF"	– 2–4 μm – Elongated cells with septae (divides by fission, not budding) – predominantly intracellular (like *Histo*) – Mimics *Histo* (but *Penicillium* is non-budding and has no pseudocapsule)		– Southeast Asia – AIDS patients
Pneumocystis jiroveci (formerly *P. carinii)*	 "teacup and saucer" in frothy exudate	– 5–8 μm cyst (seen by GMS), 1–3 μm trophozoites (seen by Giemsa) – Non-budding organisms – GMS: round and crescent (sickle)-shaped cysts (described as a "cup-and-saucer" or "crushed ping-pong balls") with two parenthesis-shaped dots (these are part of the cyst wall) – Giemsa or Diff-Quik: intracystic (up to eight) and free-roaming trophozoites	– Frothy alveolar exudate (but ~10% have a granulomatous response)	– Sites: lung – AIDS patients
Chromoblastomycosis	 "copper pennies"	– 6–12 μm – Brown (melanin-containing) organisms; Fontana-Masson+ – Thick-walled spheres with horizontal and vertical septae ("copper pennies," "medlar bodies," "sclerotic bodies")	– Overlying pseudoepithelio-matous hyperplasia is typical	– Sites: SubQ

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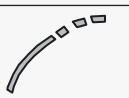
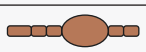
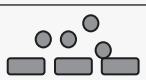
Organism or disease	Appearance (GMS or PAS)	Key histologic features	Comment
Hyphae in Tissue			
Aspergillus spp. and others **Hyalohyphomycoses** (septate nonpigmented molds, e.g., *Fusarium*)	 "slingshots "	– Thin (2–5-µm-thick) hyphae WITH septae ("septate hyphae") – Frequent dichotomous narrow-angle (45^0) branching (Y-shaped) – When invasive, tends to be angioinvasive – Hyphae tend to grow in a radial "sunburst"-like fashion – Occasional fruiting bodies (in aerated sites) – Definitive diagnosis requires cultures because in tissue, *Aspergillus* is indistinguishable from other hyaline mold, including *Pseudallescheria boydii* and *Fusarium* (both resistant to amphotericin B). Definitive morphologic speciation possible only if diagnostic fruiting bodies are present, which is rare.	Types of *Aspergillus*-related diseases include: 1. Vaso-invasive infections (sinus, lung, disseminated) in immunocompromised host. 2. Allergic bronchopulmonary aspergillosis and allergic fungal sinusitis in atopic host (eos + tigroid mucin+Charcot Leyden crystals) 3. Aspergilloma/mycetoma/fungus ball = colonization of cavities (such as sinuses or cavitary lung disease) 4. Less well-defined form is "subacute" = limited tissue invasive infection in mildly immunocompromised host (like diabetic), occurs in the sinus and lung.
Zygomycetes (*Rhizopus*, *Absidia*, *Mucor)* Disease: Zygomycosis = Mucormycosis = Phycomycosis	 "wide ribbons"	– Wide (6–50-µm-thick) hyphae with INFREQUENT or absent septae – Wide-angle (90^0) branching (branching less frequent than *Aspergillus*) – Undulating, twisting (ribbonlike), often fractured, "empty-looking" hyphae – Angioinvasive – Stain weakly with GMS and PAS; organisms best visualized by H&E – Definitive diagnosis requires culture because treated or degenerating *Aspergillus* may look like *Zygomycetes* *Note regarding the terminology: these organisms are frequently referred to collectively as "Mucor" in pathology, but *Mucor* is only one of several organisms (and not even the most common) in this group.	Aggressive vaso-invasive disease (sinus, disseminated) in immunocompromised host. This is a life-threatening emergency. Why distinguishing *Zygomycetes* vs. *Aspergillus* is important: 1. *Zygomycetes* are more aggressive 2. *Zygomycetes* are treated with amphotericin B. They are resistant to most azoles (except posaconazole).
Dermatophytes (*Microsporum* spp., *Epidermophyton* spp., *Trichophyton* spp.)		– Septate hyphae with rare branching that break into segments (arthroconidia) – 2–3 µm thick – Hyphae confined to the skin, nails, hair	Superficial infections of the and hair ("tinea" or "ringworm")
Phaeohyphomycosis (pigmented molds)		– Septate branching hyphae; may resemble *Aspergillus* in tissue though are often thinner with less branching, have constrictions at their frequent septae and vesicular swellings – Contain melanin (Fontana-Masson+) – Brown pigment sometimes (but not always) evident on H&E	SubQ and deep infections
Yeast and Hyphae in Tissue			
Candida spp.	 "sausage links and yeast"	– 3–5 µm budding yeast – 5–10 µm pseudohyphae: elongated budding yeast joined end-to-end like "sausage links"; occasionally true hyphae (no constrictions) are present – *C. glabrata* is unique in that it does not produce any hyphae; it may mimic *Histo* and other small yeast	Mucocutaneous and deep infections
Pityriasis versicolor *(Malassezia furfur)*	 "spaghetti and meatballs"	– 3–8 µm budding yeast (meatballs) and 5–10 µm fragmented hyphae (spaghetti) often arranged end-to-end – Involves epidermis only, only rarely seen in tissue (skin scraping preferred method of diagnosis)	Site: skin only
Mold-Like Branching Filamentous Bacteria			
Nocardia asteroides		– Delicate narrow (1 µm) beaded filaments; right-angle branching – Gram+, modified AFB (Fite)+, GMS+ – DDx includes *Streptomyces* (AFB–)	Deep infection in immunocompromised host
Actinomyces israelii	 "dust bunnies"	– Delicate narrow (<1 µm) branching filaments intertwined in a dense radiating meshwork – "Sulfur granules" (grossly yellow flecks; do not, in fact, contain sulfur) – Gram+, AFB–, GMS+	Normal commensal inhabitant of the oral cavity May become pathogenic in oropharynx with local tissue damage (such as dental work), may cause draining sinus tracts IUD-related infections

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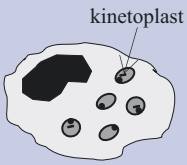
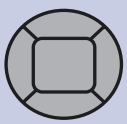
Yeastlike Organisms in Tissue			
	Organism	*Key histologic features*	*Comment*
Protozoa	***Leishmania spp*** 	– 2–4 µm round to oval aflagellate amastigotes (extravascular form of organisms) – Amastigotes are intracellular – Transverse paranuclear bar-like kinetoplast – *Leishmania* is a close mimic of *Histoplasma* (look for kinetoplast) – Organisms stain lightly in H&E – GMS–, PAS–, Giemsa+	Visceral leishmaniasis (kala-azar): – Middle East, Africa, India – Sites: reticuloendothelial system (liver, spleen, bone marrow) Cutaneous leishmaniasis: Old World ("oriental sore") and New World ("chicle ulcer") Mucocutaneous leishmaniasis: Central and South America
	Trypanosoma cruzi	– Organisms in tissue look identical to *Leishmania* spp. – *T. gambiense* and *T. rhodesiense* (African trypanosomiasis) are confined to blood and do not invade tissue	*T. cruzi* (Chagas disease): – Central and South America – Usual sites: heart, colon, esophagus
	Toxoplasma gondii	– 5–7 µm crescent-shaped tachyzoites (non-encysted organisms in tissue) – 10–50 µm pseudocysts packed with 2–3 µm round bradyzoites – Basophilic in H&E (unlike yeast) – GMS+, PAS+, Giemsa+	– Worldwide disease, cat vector – Sites: disseminated disease (especially brain) in immunosuppressed patients
	Cryptosporidium	– 2–6 µm round organisms in the brush border of small bowel mucosa – Giemsa+	Chronic diarrhea in immunosuppressed patients
	Cyclospora	– 8–10 µm oocysts in stool – Modified acid fast or safranin stain (stool)+ – Autofluorescence+	
	Cystoisospora belli	– 25–30 µm elliptical organisms interposed between adjacent enterocytes – Giemsa+	
	Microsporidium	– 1–3 µm round organisms in the cytoplasm of enterocytes – Invisible by H&E – Gram+	
Algae	***Prototheca* spp.** 	– 2–12 µm – Sporulating forms are sporangia with up to 20 polygonal or wedge-shaped endospores whose cell walls mold together ("morulas") – GMS+, PAS+	– Two human infections: cutaneous (usually immunosuppresed) and olecranon bursitis (usually otherwise healthy with a history of trauma)
References: [8–10]			

Quick Reference for Histological Identification of Viruses

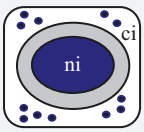
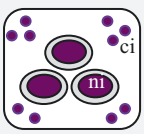
In general, nuclear inclusions are associated with DNA viruses (HSV, CMV, adenovirus, JC, and BK viruses). One major exception is CMV in that in addition to nuclear inclusions, it also forms cytoplasmic inclusions. Some DNA viruses do not have any recognizable cytopathic effects (EBV, HHV8). Note that HPV does not manifest as inclusions but has a unique cytopathic effect (see below).

RNA viruses as a rule do not have recognizable cytopathic changes; few do have cytoplasmic inclusions (RSV, Negri bodies in rabies). Measles is an exception in that it is an RNA virus that forms nuclear inclusions.

Nuclear inclusions of virally infected cells fall into two morphologic categories:

1. **Cowdry type A**: eosinophilic "owl-eye" nuclear inclusion (as in CMV)
2. **Cowdry type B**: (aka "smudge cells") nucleus with a "homogenized, ground glass" chromatin and obliterated nuclear detail

Note that most DNA viruses (HSV, adenovirus) can have nuclear inclusion of either Cowdry A and/or Cowdry B type even within the same lesion. Exception is CMV in that it forms exclusively type A inclusions.

Virus	Appearance	Nuclear inclusions	Cytoplasmic inclusions	Specific features	Infected cell type	Clinical
HSV	 "eggs in a basket" or "pomegranate seeds"	+ (Cowdry A or B), pink, steel gray, or purple	–	The 3 M's: **M**ultinucleation, **M**olding, **M**argination of chromatin (peripheral clearing or "halo effect")	Squamous and some glandular epithelial cells (look at the periphery of an ulcer on mucosal surfaces)	Gingivostomatitis and genital lesions in immunocompetent host. Opportunistic infection of any body site (pneumonia, esophagitis, neurons in encephalitis)
CMV	 "owl-eye nuclear inclusion and cytoplasmic speckles"	+ (Cowdry A), blue	+ (blue speckles)	Nuclear and cytoplasmic enlargement Nuclear inclusion has a prominent halo ("owl eye"), which corresponds to marginated chromatin pushed aside by viral particles.	Stromal and endothelial cells (look at the ulcer base); rarely in epithelial cells	Opportunistic infection of any body site (lung, bowel, retina, neurons in encephalitis)
Adenovirus		+ (Cowdry A or B), blue	–		Epithelial cells (bronchial cells and pneumocytes in the lung)	Opportunistic infections (bladder, kidney, lung, bowel)
HPV	 "koilocyte"	–	–	Clear perinuclear vacuole (Greek *koilos* = hollow), wrinkled (raisin-like) nucleus, binucleation (common), condensed keratohyaline granules typical in skin	Squamous cells	Papillary lesions (warts, condyloma, laryngeal papillomas) and squamous dysplasia and intraepithelial neoplasia (genital organs and rectum)
JC and BK (polyoma)	 "decoy cell"	+ (Cowdry B), blue	-	Nuclear enlargement Non-haloed smudgy (type B) inclusion	JC – brain BK – urothelium (mimics CIS in urine; "decoy" cells)	JC – PML BK – cystitis in immunosuppressed
Measles	 "Warthin-Finkeldey giant cell"	+ (Cowdry A or B), pink	+ (pink speckles)	Giant cells with multinucleation	Depends on the site: -Lung: epithelial cells, most commonly bronchial -Lymph node: lymphoreticular cells (infected cells in lymph node are called Warthin-Finkeldey giant cells) -Brain: oligodendroglia	Pneumonitis, lymphadenitis, SSPE
RSV		–	+ (large pale-pink globs)	Giant cells with multinucleation No nuclear inclusion (this is an RNA virus)	Epithelial cells	Bronchiolitis and pneumonia in children (rarely biopsied)

Abbreviations: *ni* nuclear inclusion, *ci* cytoplasmic inclusion, *PML* progressive multifocal leukoencephalopathy, *SSPE* subacute sclerosing panencephalitis

Tumor Viruses: Quick Reference for Tumor/Viral Associations

Detection of viral molecules is a very helpful adjunct in the diagnosis of the virally induced tumors. In tissue sections, viral proteins can be detected by immunohistochemistry (e.g., EBV-LMP), or viral nucleic acids may be identified by in situ hybridization/ISH (e.g., EBER ISH and HPV by DNA-ISH and more recently RNA- ISH, which is much more sensitive). p16 is NOT a viral protein but an endogenous cell cycle protein that is markedly overexpressed as a result of high-risk HPV infection. In cervical cytology, the specimens are tested for HPV by a DNA-based method (hybrid capture).

Virus	Tumor associations		Detection in tissue
EBV	**Epithelial lesions:** – Nasopharyngeal carcinoma (NPC), aka lymphoepithelial carcinoma (= lymphoepithelioma [LE]) and LE-like carcinomas: ○ EBV (+): NPC and LE-like carcinomas of upper aerodigestive tract (lung, thymus, salivary gland) and stomach ○ EBV (−): LE-like carcinoma of non-aerodigestive tract (bladder, breast, skin, cervix) – Oral hairy leukoplakia – Gastric adenocarcinoma (5%)		1. EBER (EBV encoded early RNA). Most sensitive marker for EBV (in situ hybridization method). IDs all EBV-related tumors. 2. EBV-LMP (late membrane protein). Less sensitive than EBER. IDs PTLD and AIDS-related lymphomas, variable in NPC, Hodgkin, and Burkitt lymphoma, usually negative in plasmablastic lymphoma 3. EBNA (EBV nuclear antigen). Least sensitive marker. IDs PTLD and AIDS-related lymphomas only.
	Lymphoid/heme lesions: – Infectious mononucleosis – Posttransplant lymphoproliferative disease (PTLD) – Classic Hodgkin lymphoma (Mixed cellularity – 70%, AIDS-related) – Non-Hodgkin lymphoma: ○ Burkitt lymphoma (endemic 100%; sporadic 20%) ○ Nasal-type NK/T-cell lymphoma (>95%) ○ Aggressive NK cell leukemia ○ Angioimmunoblastic T-cell lymphoma ○ Lymphomatoid granulomatosis (>95%) ○ CNS lymphoma in AIDS (95%) ○ Plasmablastic lymphoma (HIV) ○ Primary effusion lymphoma (has both EBV and HHV8) ○ EBV+ DLBCL – Germinotropic lymphoproliferative disorder (has both EBV and HHV8) – Inflammatory pseudotumorlike follicular dendritic cell sarcoma – EBV-positive mucocutaneous ulcer		
	Smooth muscle tumors in immunosuppressed (AIDS, transplant)		
HPV	**Female genital tract:** – Squamous dysplasia and carcinoma of the cervix, vagina, vulva (simplex/differentiated VIN and associated SqCC occur in the setting of lichen sclerosus and other dermatoses in older women and are HPV-unrelated)	HSIL and associated SqCC caused by high-risk HPV (16, 18, 31, 33) LSIL is caused by – low-risk HPV (6, 11) in 20% – high-risk HPV in 80% (therefore, high-risk HPV does not distinguish HSIL and LSIL)	1. In situ hybridization for HPV (DNA or RNA) 2. IHC for p16 is a surrogate marker of high-risk HPV Detection of HPV may be used to identify anogenital or oropharyngeal origin of metastatic SqCC of unknown primary. HPV-related SqCC of some (but not all) sites have basaloid morphology: – Sites where HPV-related SqCC are basaloid: oropharynx, penis, vulva – Sites where HPV-related SqCC are either basaloid or conventional: cervix, anus – Sites where basaloid SqCC are unrelated to HPV: breast, lung, non-oropharyngeal head and neck
	– Cervical adenocarcinoma (in situ and invasive)	HPV 18 > 16	
	Penis: – Squamous cell carcinoma, warty and basaloid type (verrucous and papillary SqCC are HPV-unrelated)	HPV 16	
	– Bowenoid papulosis and Erythroplasia de Queyrat	HPV 16	
	Anus: Squamous neoplasia (in situ and invasive) – analogous to cervix	HPV 16, 18	
	Head and neck: – Squamous cell carcinoma of the oropharynx (tonsil and base of tongue)	HPV 16, 18	
	– Laryngeal papillomatosis	HPV 6, 11	
	– Focal epithelial hyperplasia (Heck disease) of oral mucosa	HPV 13, 32	
	– Sinonasal HPV-related multiphenotypic CA	HPV33 and others (not 16 or 18)	
	Mucocutaneous: – Warts (verruca)	HPV 1, 2, 4, 7	
	– Condyloma acuminatum (genital sites)	HPV 6, 11	
HHV8	Kaposi sarcoma, primary effusion lymphoma (also has EBV), germinotropic lymphoproliferative disorder (also has EBV), Castleman disease (multicentric)		HHV8 can be detected by IHC
HTLV1	Adult T-cell leukemia/lymphoma		
Hepatitis B	Hepatocellular carcinoma (Hep C causes HCC indirectly – virus is not present in tumor cells)		HBsAg, HBcAg – rarely used for tumor Dx
Merkel cell polyomavirus	Nearly all Merkel cell carcinomas		Viral antigen can be detected in Merkel cell CA by IHC, (−) in small cell carcinoma

Quick Electron Microscopy Reference for Tumors and Select Non-tumor Diagnoses

By Marina K Baine

General Cell Types	
Epithelial	Desmosomes
Neuroendocrine	Neurosecretory (dense-core) granules
Fibroblast	Abundant rough endoplasmic reticulum
Muscle	Actin filaments
Skeletal muscle	Ribosome-filament complexes Z-band
Smooth muscle	Dense bodies (subplasmallemal) Filaments
Endothelial	Weibel-Palade bodies (elongated, "pear-shaped" storage granules with microtubule-like inclusions appearing striated) Pinocytotic vesicles
General Tumor Types	
Carcinoma	Desmosomes (tight junctions)
Adenocarcinoma	Short luminal ("intestinal type") microvilli Extra- and intracellular lumina Mucin granules Tight junctions
Squamous cell carcinoma	Well-formed intercellular junctions Tonofilaments
Melanoma	Pre-melanosomes and melanosomes
Mesothelioma	Long and thin microvilli Tight junctions Long desmosomes Perinuclear tonofilament bundles
Lymphoma	Abundant polyribosomes Paucity of organelles Devoid of cell junctions
Sarcoma	Absence of true desmosomes and true lumens (most) (Other features vary depending on subtype)
Leukemia	Lineage dependent
Lymphoid	Scant cytoplasm Free ribosomes and polyribosomes Paucity of cell organelles
Myeloid	Abundant cytoplasm Prominent Golgi and rough endoplasmic reticulum +/– Azurophilic granules
Specific Tumor Types and Tumorlike Lesions with Distinctive EM Findings	
Leydig cell tumor	Reinke crystals
Sertoli cell tumor	Charcot-Bottcher crystals
Alveolar soft part sarcoma	Membrane-bound rhomboid crystals with a lattice pattern with a 10-nm periodicity in fibrils (crystal precursor is Golgi) Numerous electron dense vesicles near Golgi
Granular cell tumor	Pleomorphic secondary lysosomes Basal lamina around cell groups Angulate lysosomes ("Gaucher-like") in stromal fibrohistiocytic cells
Schwannoma	Luse bodies (long-spaced collagen) Reduplicated basal lamina
Langerhans cell histiocytosis	Birbeck granules ("tennis racket")
Rosai-Dorfman disease	Emperipolesis of nucleated and nonnucleated blood cells (also seen on light microscopy)
Selected Storage Disorders	
Gaucher disease	Angulated lysosomes
Tay-Sachs disease	Laminated (concentric structure of membranous cytoplasmic bodies)
Niemann-Pick disease	Zebra bodies (aka myelin figures)
Fabry disease	Zebra bodies (aka myelin figures)
Selected Viruses	
VZV/HSV/CMV	Bull's eye appearance in cytoplasm (indistinguishable by EM)
Adenovirus (and other non-enveloped viruses)	Honeycomb (viral particles arranged in paracrystalline arrays)
Papovavirus	Spaghetti and meatballs (virions are both filamentous and spherical)