OSSIFYING FIBROMA

Clinical:
-Benign jaw tumors, juvenile variant typically arises in maxilla and paranasal sinus walls; juvenile cases associated with more aggressive behavior

Histology:
-Islands and trabeculae of bone set in fibroblastic background
-May be identical to fibrous dysplasia; distinction is made on clinical/radiographic grounds (OF=circumscribed mass, FD=indistinct)
-Psammomatoid variant contains innumerable acellular to sparsely cellular mineralized deposits known as “ossicles,” may fuse to form trabeculae

Molecular/Genetic:
-Multiple tumors may be seen in hereditary hyperparathyroid-jaw tumor syndrome, mutation in HRPT2 on chromosome 1q encoding parafibromin

LOBULAR CAPILLARY HEMANGIOMA ("Pyogenic Granuloma")

Clinical:
-Polypoid growth often of skin or mucous membranes, can occur in any age, may be preceded by trauma, common in pregnancy

Histology:
-Small vessel proliferation divided into lobules by fibrous connective tissue
-Vessels lined by plump endothelial cells, surrounded by pericytes
-Polypoid examples may have an in-growing collarette of hyperkeratotic epidermis

Molecular/Genetic:
-Clonal evidence indicates that these are true neoplasms therefore the name “pyogenic granuloma” is inappropriate

CALCIFYING APOPNEUROTIC FIBROMA

Clinical:
-Ill-defined, painless masses on the hands and feet of children aged 10-15
-Usually <3 cm, may reach 5 cm

Histology:
-Fibrous tissue surrounding cellular nodules with central chondroid tissue and calcification
-Cellular component is comprised of cells with plump oval vesicular nuclei, often palisade around calcified centers
-Fibrous component is comprised of small mature spindled fibrocytes which may infiltrate surrounding muscle, nerves, and fat

FIBROMA OF TENDON SHEATH

Clinical:
-Well-circumscribed nodules associated with tendon or tendon sheath on fingers, wrists, and/or hands, usually male patients aged 30-50

Histology:
-Densely collagenized, paucicellular
-Bland spindled cells with uniform, elongate nuclei; pleomorphic cells may be seen in rare cases and are not clinically significant
-Slit-like vascular spaces often present

Molecular/Genetic:
-Probably reactive, rather than true neoplasm; may represent burnt out giant cell tumor of tendon sheath
DERMATOFIBROSARCOMA PROTUBERANS

Clinical:
-Dermal or subcutaneous tumor of the trunk or proximal extremities, usually in adults; “intermediate” malignancy; metastases are rare (~3%)

Histology:
-Dense aggregates of spindled cells in storiform or “cartwheel” patterns, infiltrative into dermis; strongly CD34-positive
-“Bednar tumor”=pigmented variant, must be distinguished from melanoma

Molecular/Genetic:
- Closely related to the pediatric tumor “giant cell fibroblastoma”
-Both tumors bear the t(17;22) translocation, fuses COL1A1 to PDGF

GIANT CELL TUMOR OF TENDON SHEATH

Clinical:
- 2 Forms: 1) Nodular Tenosynovitis (NT) occurs in hands with occasional local recurrence (20%); 2) Pigmented Villonodular Synovitis (PVNS) affects knee/ankle joints and is quite locally aggressive

Histology:
-NT: circumscribed, cellular, multinucleated benign giant cells, inflammatory cells, hemosiderin, cleftlike spaces, positive for CD68, scattered desmin
-PVNS: similar to NT but with florid papillary synovitis and extension into soft tissue

Molecular/Genetic:
-NT has been shown to be polyclonal
-Both tumor types contain COL6A3-CSF1 gene fusion

GLOMUS TUMOR

Clinical:
- Painful purple nodules, often subungual and rarely on trunk; pain may be precipitated by cold exposure

Histology:
-Sheets of pericyte-derived cells with epithelioid appearance, eosinophilic cytoplasm, and small round nuclei with fine chromatin
-Vascular spaces interspersed throughout; may be huge (glomangioma)
-Positive for smooth muscle actin (SMA) and muscle-specific actin (MSA)

Molecular/Genetic:
-Glomangioma may be multiple in cases of autosomal dominant inheritance

EPITHELIOID SARCOMA

Clinical:
- Classically presents as subcutaneous or dermal nodules occurring from wrist to elbow of a young adult

Histology:
-Admixed spindled and rounded eosinophilic cells with small nucleoli, occasional nucleoli arranged in nodular patterns with central necrosis, often with accompanying inflammatory infiltrate; may mimic rheumatoid nodules
- Proximal type contains sheets of cells with prominent nucleoli, resembles poorly-differentiated carcinoma
-CK and EMA positivity are common; CD34 positive in half; INI1 is LOST
SYNOVIAL SARCOMA

Clinical:
- Extremities of young adults; childhood cases may show prolonged survival

Histology:
- Biphasic: glandular elements with eosinophilic cytoplasm, oval nuclei, secrete mucicarmine/PAS-positive substance; stromal element comprised of “blastic” looking spindled cells
- Monophasic: spindled stromal cells in herringbone or hemangiopericytoma-like pattern, rare epithelioid cell clusters highlighted by reticulin, CK
- Stain for CK7, CK19, EMA, BCL-2, CD99, rarely S100, calponin, and SMA
- Calcified variant (commonly biphasic) has more favorable outcome
- Thin spaces lined by microvilli seen on EM

Molecular/Genetic:
- t(X;18) due to SYT-SSX1 or SYT-SSX2 fusion genes are specific

LANGERHANS CELL HISTIOCYTOSIS

Clinical:
- Primarily a childhood disease
- Letterer-Siwe disease: babies <2, multifocal skin &/or systemic lesions
- Hand-Schüller-Christian disease: exophthalmos, bony lytic lesions, diabetes insipidus (due to pituitary stalk infiltration)
- Eosinophilic granuloma: unifocal disease, older children and adults

Histology:
- Aggregates of cells with eosinophilic cytoplasm, grooved, folded, and reniform nuclei; extravasated erythrocytes and inflammatory infiltrate with eosinophils often present
- S-100 protein, CD1a, vimentin, HLA-Dr, peanut agglutinin, CD4, PLAP
- Birbeck granules seen on EM

Molecular/Genetic:
- Letterer-Siwe is autosomal recessive

JUVENILE XANTHOGRANULOMA

Clinical:
- Cutaneous/subcutaneous nodules most often in head and neck of children
- Most common extracutaneous site is eye; rarely arise in deep soft tissue
- Often spontaneously involute

Histology:
- Early lesions show aggregates of macrophages containing lipids, mature lesions are comprised of vacuolated, spindled and/or oncocytic cells
- Classic (but not necessary) finding is Touton giant cell: core of eosinophilic cytoplasm surrounded by a wreath of nuclei and outer lipid layer
- Stain for vimentin, CD68, lysozyme, factor XIIIa

PLEXIFORM FIBROHISTIOCYTIC TUMOR

Clinical:
- Deep dermal and subcutaneous nodules, affects children and young adults, female predominance
- Local recurrence in >1/3, local nodal metastases rare

Histology:
- Comprised of fibrohistiocytic cells and multinucleated giant cells, surrounded by a rim of fibrous tissue
- Resembles giant cell tumor of tendon sheath but superficial location excludes this
DERMATOFIBROMA (“Fibrous Histiocytoma”)

Clinical:
- Firm, round papules on lower legs, arms, trunk

Histology:
- “Lens-shaped” dermal proliferation of spindled cells with admixed thickened collagen bundles, periphery shows collagen trapping, overlying epidermis is typically acanthotic, may see stromal induction mimicking BCC
- Variants include deep penetrating, lipidized, aneurysmal, fibrotic, and granular cell dermatofibromas, as well as tumors with monster cells
- Lipidized variant shows foamy macrophages, hemorrhage, and Touton-like giant cells

Molecular/Genetic:
- Recent evidence suggests neoplastic but some argue reparative

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OVARIAN EMBRYONAL CARCINOMA

Clinical:
- 3% of primitive ovarian GCT, children and young adults,
- Can be associated with isosexual precocity, elevated hCG and AFP

Histology:
- Identical to testicular counterpart: solid masses, glands, and papillae lined by large cells with amphophilic or vacuolated cytoplasm, well-defined cell membranes, round, vesicular, often pleomorphic nuclei
- Scattered syncytiotrophoblastic giant cells

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OVARIAN YOLK SAC TUMOR (“Endodermal Sinus Tumor”)

Clinical:
- 20% of primitive ovarian GCT, rare after age 40, elevated AFP

Histology:
- Primitive cells with clear cytoplasm (contains glycogen and lipid), hyperchromatic, irregular nuclei, PAS-positive hyaline bodies, arranged in a variety of patterns, great mimicker
- Reticular pattern most common, others include hepatoid, micrystal, macrystal, polyvesicular vitelline, endometrioid-like, solid, papillary, adenofibromatous
- Schiller-Duval Bodies (papillae w/ central core containing vessel)

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OVARIAN CHORIOCARCINOMA

Clinical:
- 1% of primitive ovarian GCT, hCG elevation leads to isosexual precocity when present in children, menstrual abnormalities in adults
- Propensity to metastasize esp. to lungs but very chemoresponsive with apparent cures even after metastasis

Histology:
- Biphasic, usually plexiform proliferation of cytotrophoblasts and syncytiotrophoblasts with dilated vessels and associated hemorrhage
- Intermediate trophoblastic cells may be present
- Must be distinguished from other germ cell tumors with isolated syncytiotrophoblastic cells
**OVARIAN IMMATURE TERATOMA**

*Clinical:*
- 20% of primitive ovarian GCT, affect children and young adults
- Tends to spread through peritoneum, benign implants may continue to grow after initial surgery *(growing teratoma syndrome)*

*Histology:*
- Immature, embryonic-type tissue can be focal or predominant, consists primarily of **neuroectodermal elements** including **rosettes** and **tubules**, mitotically active glia, GMB-like areas
- May see associated implants of mature glial tissue *(peritoneal gliomatosis)*
- Graded from 1-3 based on amount of immature tissue

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**DYSGERMINOMA**

*Clinical:*
- Most common primitive ovarian GCT (50%), most often in women <30, rare over 50 or under 5, malignant but chemosensitive
- Elevated **lactate dehydrogenase** (isoenzymes 1 and 2)

*CP PEARL: There are 5 LD isoenzymes; 1 and 2 migrate fastest on electrophoresis*

*Histology:*
- Identical to **seminoma** in testes, comprised of diffuse or insular arrangements of uniform, round tumor cells with clear or eosinophilic cytoplasm, central nucleolus, prominent nucleoli, **discrete cell membranes**, stroma comprised of **fibrous septae**, robust **lymphocyte** infiltration, may see **granulomas**, **syncytiotrophoblastic giant cells**

**OVARIAN SERTOLI-LEYDIG CELL TUMOR**

*Clinical:*
- <0.2% of all ovarian tumors, average age 25, half of patients show hirsutism or virilization

*Histology:*
- Well-differentiated tumors are comprised of **hollow to solid tubules** with a significant component of **stromal Leydig cells**. Crystals of Reinke are rare; tumors with intermediate and poor differentiation have less well-organized Sertoli component
- **Heterologous mucinous elements** are common
- **Retiform tumors** with elongated tubules and papillae simulate the **rete testis** and are seen in young patients, often **cystic**

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**JUVENILE GRANULOSA CELL TUMOR**

*Clinical:*
- Usually occur in children/young adults but occasionally seen in older women, most patients present at **stage I**

*Histology:*
- Sheets and nodules of cells with abundant eosinophilic or vacuolated cytoplasm, hyperchromatic often **atypical** nuclei, and prominent nucleoli
- In contrast to adult type, **grooves are rare**
- Variably sized **follicles** are prominent and contain **mucicarmine**+ **secretions**. Basophilic mucinous fluid mat be seen in background
INFANTILE FIBROSARCOMA (“Congenital fibrosarcoma”)

Clinical:
- Patients must be **under 10 years old**, most are **infants**, involves trunk and extremities (usually distal)

Histology:
- **Broad fascicles** of uniform malignant spindled **fibroblasts** or **myofibroblasts** bearing scant cytoplasm and elongate nuclei with hyperchromatic granular chromatin; **round cell** areas may be present; stroma is scant
- **May stain with actin** (30%); **negative** for desmin, CD34, S100

Molecular/Genetic:
- Bears the **t(12;15)** translocation leading to **ETV6-NTRK3** gene fusion
- This translocation is also seen in **congenital mesoblastic nephroma**

FIBROUS HAMARTOMA OF INFANCY

Clinical:
- Superficial soft tissue tumors in patients <4 years, **male** predilection, usually **single**, low risk of recurrence

Histology:
- **Triphasic** tumor comprised of organoid arrangements of fibrous trabeculae, disorganized **mature fat**, and islands of immature mesenchymal cells
- Mitotic figures rare
- Overlying skin may show hyperplasia, duct dilatation, squamous metaplasia

INFANTILE DIGITAL FIBROMA (“Inclusion Body Fibromatosis”)

Clinical:
- Dorsal digital dermal or subcutaneous nodules in patients <1 year
- More than half recur after excision

Histology:
- Poorly circumscribed proliferation of fascicles and sheets of fibroblastic/myofibroblastic spindle cells embedded in a collagen matrix, infiltration of deep dermis and subcutis is common
- **Perinuclear round eosinophilic inclusions** are **negative** for PAS, positive for SMA and vimentin; approximately the size of erythrocytes

Molecular/Genetic:
- Rare cases associated with syndrome that includes facial pigmented dysplasia, focal dermal hypoplasia, metacarpal/tarsal disorganization, and limb malformations

MYOFIBROMA (“Infantile Myofibromatosis”)

Clinical:
- Often discovered at **birth**, patients usually **under 2**
- Commonly **multiple**, most often in skin, subcutaneous tissue, and skeletal muscle of head and neck, bone and visceral involvement can occur

Histology:
- **Biphasic** tumor comprised of nodules of **mature** and **immature myofibroblastic cells** with hemangiopericytoma-like vessels,
- **Zonation** is typical with light-staining mature elements arranged around periphery, dark-staining immature elements at center; **Actin** positive

Molecular/Genetic:
- Rare familial cases exist, autosomal dominant inheritance
- Nonspecific **chromosome 8** abnormalities identified, **lack** the 12;15 translocation seen in infantile fibrosarcoma

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- **Perinuclear round eosinophilic inclusions** are **negative** for PAS, positive for SMA and vimentin; approximately the size of erythrocytes

Molecular/Genetic:
- Rare cases associated with syndrome that includes facial pigmented dysplasia, focal dermal hypoplasia, metacarpal/tarsal disorganization, and limb malformations
DESMOID FIBROMATOSIS

**Clinical:**
- Large mass, often of abdomen or trunk, in a patient **over age 5**

**Histology:**
- Uniformly cellular tumor comprised of haphazard arrangements or fascicles of fibroblasts with small, often elongate nuclei, scant cytoplasm; cells **blend imperceptibly into background collagen**; slit-like vessels
- Peripheral infiltration of skeletal muscle is an important feature
- Beta-catenin nuclear positivity

**Molecular/Genetic:**
- Evidence suggests that they are clonal therefore likely neoplastic
- Mesenteric and postoperative lesions may occur in **Gardner Syndrome**

INFANTILE FIBROMATOSIS

**Clinical:**
- Infiltrative tumors of the head, neck, or thigh in patients **under 8 years**

**Histology:**
- 2 types: 1) Adult type is identical to adult desmoid fibromatosis 2) Diffuse mesenchymal type contains uniform bland cells in myxoid stroma, nuclei may be round, oval, or spindled; often contains fat; many muscle fibers remain intact; can invade bone

PRIMITIVE NEUROECTODERMAL TUMOR

**Clinical:**
- Patients <30; can be peripheral or arise on trunk, chest wall (Askin tumor)

**Histology:**
- Sheets and lobules comprised of **small round cells** with uniform, round to oval, finely stippled or vesicular nuclei; **fibrous septae** common, CD99+
- Intermediate filaments present on EM: marks pluripotency of cells
- PAS-positive, diastase sensitive, indicating glycogen
- Rosettes and neural markers (neurofilament, synaptophysin, chromogranin, S100) are present, distinguishing from Ewing

**Molecular/Genetic:**
- Same family as **Ewing sarcoma**; both tumors have **EWS-FLI-1 fusion** via t(11;22) or, less commonly, t(7;22) or t(21;22)

EWING SARCOMA

**Clinical:**
- Bone tumors arising in patients <30

**Histology:**
- Sheets and lobules comprised of **small round cells** with uniform, round to oval, finely stippled or vesicular nuclei; **fibrous septae** common, CD99+
- Intermediate filaments present on EM: marks pluripotency of cells
- PAS-positive, diastase sensitive, indicating glycogen
- Lack evidence of neural differentiation, distinguishing from PNET

**Molecular/Genetic:**
- Same family as PNET; both tumors have **EWS-FLI-1 fusion** via t(11;22) or, less commonly, t(7;22) or t(21;22)
DESMOPLASTIC SMALL ROUND CELL TUMOR

Clinical:
- Extremely aggressive, usually abdominal mass in predominantly male young adult patients

Histology:
- Nests of tumor cells set in prominent desmoplastic stroma; tumor cells have scanty cytoplasm, indistinct borders, and spindled shape with uniform small, hyperchromatic, oval nuclei and inconspicuous nucleoli.
- Immunostains reveal a unique combination of epithelial, neural, and muscle markers with CK, EMA, NSA, desmin, and vimentin positivity; WT1 is also often positive *because fetal mesothelium also shows dual CK and desmin positivity, DSRCT may represent a “mesothelioblastoma”

Molecular/Genetic:
- t(11;22) translocation similar, but not identical, to the one seen in Ewing/PNET; leads to EWS-WT1 gene fusion

ALVEOLAR Rhabdomyosarcoma

Clinical:
- Aggressive, older patients (adolescents) and worse prognosis than embryonal subtype, affects extremities and trunk

Histology:
- Tumor cells float in or hug the periphery of alveoli-like spaces demarcated by fibrous septae; most cells lack cytoplasm, rare eosinophilic cells present; occasional multinucleated giant cells with a wreath of nuclei
- Solid variant lacks spaces, can be identified by the multinucleated giant cells which are absent in embryonal

Molecular/Genetic:
- t(2;13)(q37;q14); del(13)(q14)
- PAX7-FKHR tumors carry a better prognosis than PAX3-FKHR tumors

EMBRYONAL Rhabdomyosarcoma

Clinical:
- Aggressive soft tissue tumors in children (orbit, head and neck, GU, retroperitoneum) and adolescents (paratesticular, extremities)
- Most common type of rhabdomyosarcoma; most childhood cases favorable (e.g. may be cured by chemo), worse prognosis in adolescents

Histology:
- Sheets of poorly to moderately differentiated rounded cells with frequently eccentric nuclei, eosinophilic granular cytoplasm without tapering, crossstriations are uncommon
- Botryoid Rhabdomyosarcoma variant occurs in lumen/space (GU/genital tract, conjunctiva); myxoid, dense cambium layer beneath epithelium

Molecular/Genetic:
- t(8;11)(q12;q21); trisomy 11; del(11)

CHONDROBLASTOMA

Clinical:
- Benign tumors, usually ends of long bones with epicenter in the epiphysis; extension to metaphysis common; well-circumscribed on XR
- Patients usually in second decade, older if site is skull
- Usually benign behavior but may recur locally and rare lung mets

Histology:
- Mononuclear cells mixed with giant cells, mononuclear cells often have grooves, clear or pink cytoplasm, distinct outlines, chicken wire calcification is classic, chondroid differentiation present in vast majority
- >1/3 associated with secondary aneurysmal bone cyst
OSTEOBLASTOMA

Clinical:
- Benign, tumor of young (2nd decade), often male patients, often involves spine, diaphysis of long bones, imaging shows sclerotic rim
- Distinguished from osteoid osteoma only on the basis of size >1.5 cm; some report that it is also less responsive to aspirin that osteoid osteoma

Histology:
- Nidus of anastomosing bony trabeculae rimmed by osteoblasts; nidus is grossly red and granular; spaces between trabeculae show capillary proliferation

FIBROUS DYSPLASIA

Clinical:
- Fibroosseous lesion in the jawbones, ribs, and femurs of patients <30
- On a spectrum with ossifying fibroma and cement-ossifying fibroma (COF); FD has less well-defined borders has a higher recurrence rate

Histology:
- Hypocellular proliferation of plump spindled cells with collagen production, irregularly shaped, often curvilinear trabeculae of woven bone (“C’s and S’s”)
- Osteoblastic rimming is rare (unlike in ossifying fibroma)

Molecular/Genetic:
- Albright Syndrome: multifocal fibrous dysplasia with skin pigmentation, endocrine hyperactivity, and precocious puberty
- Mazabraud Syndrome: fibrous dysplasia associated with intramuscular myxomas

NONOSSIFYING FIBROMA ("Metaphyseal fibrous defects")

Clinical:
- Usually incidental findings, often but not exclusively in young (<20) male patients; located in metaphysis of long bones, esp. tibia and distal femur
- XR shows lucent, elongated cortical +/- medulla defect, scalloped edge

Histology:
- Spindle cell proliferation with storiform arrangement with scattered benign giant cells; may see hemosiderin pigment, foam cells, cholesterol crystals

Molecular/Genetic:
- Probably not a true neoplasm

OSTEOSARCOMA

Clinical:
- High-grade malignancy primarily in metaphysis of long bones in children and adolescents, male predominance; propensity for lung mets
- XR shows destructive lesion with soft tissue infiltration, reactive new bone at junction of cortex where periosteum is lifted off (=Codman triangle)

Histology:
- High grade spindle cell proliferation produces fine, lacelike osteoid matrix, may see scattered benign giant cells
- Chondroid differentiation predominant in 25% of cases (chondroblastic osteosarcoma)
- Fibroblastic variant shows very little matrix production
- Extent of necrosis after chemotherapy has prognostic impact
WILMS TUMOR ("Nephroblastoma")

**Clinical:**
- Peak incidence **2-5 years**, mets to the L's (liver, lung, regional lymph nodes)
- May secrete von Willebrand factor, renin, epo, and NSE

**Histology:**
- Most are **triphasic** with blastemal (nested, diffuse, or basaloid), stromal (immature myxoid/spindle mesenchymal cells, mature skeletal muscle), and epithelial (usually tubular) elements; some cases are mono or biphasic.
- 5% show **anaplasia**, the only criterion for **unfavorable histology**
- The presence of nephrogenic rests imparts risk for opposite kidney

**Molecular/Genetic:**
- Anaplasia correlates w/ p53 gene muts; LOH at 1p & 16q: worse prognosis
- Beckwith-Wiedemann: WT + hemihypertrophy, macroglossia, abdominal wall defects; WAGR: WT + aniridia and genital abnormalities; Denys-Drash: WT + pseudohermaphroditism, severe glomerulopathy

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CLEAR CELL SARCOMA OF KIDNEY

**Clinical:**
- Rare (3% pediatric renal tumors), propensity for **widespread metastasis** (formerly called “bone metastasizing renal tumor of childhood”), peak incidence years 2-3

**Histology:**
- 1x diagnosis: uniform, **pale blue** tumor with **scalloped** border and **thick capsule**; higher power shows evenly distributed **vascular septae** subdividing cords and nests of **polygonal tumor cells** with **indistinct borders**, fine chromatin; **mucopolysaccharide vacuoles** are a distinct feature
- Variant patterns include **epithelioid**, **spindled**, **myxoid**, **sclerosing**, **palisading** and can mimic a variety of other tumors

**Molecular/Genetic:**
- t(10;17) has been described in multiple cases

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RHABDOID TUMOR

**Clinical:**
- Rare tumor of **infants**, often associated with **hypercalcemia** due to parathromone or prostaglandin E2 secretion
- 15% are associated with posterior fossa AT/RTs, dermal **neurovascular hamartomas** described

**Histology:**
- Monomorphous proliferation of large rounded or polygonal cells with abundant cytoplasm, large vesicular nuclei, extremely **prominent nucleoli**, and **cytoplasmic inclusions**; EM reveals that inclusions are comprised of whorled **intermediate filaments**
- **Loss of INI1** expression by IHC

**Molecular/Genetic:**
- Mutation, deletion, or whole chromosome loss of **chromosome 22** leads to inactivation of **hSNF5/INI1** gene

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METANEPHRIC STROMAL TUMOR

**Clinical:**
- Clinically benign renal tumors which, along with metanephric adenofibroma and metanephric adenoma, appear to be hyperdifferentiated relatives of WT

**Histology:**
- Unencapsulated tumor comprised of **subtly infiltrative** spindled cells with thin, hyperchromatic nuclei, indistinct cytoplasmic extensions; forms **onionskin** rings around native renal elements, entrapped glomeruli can show **juxtaglomerular cell hyperplasia** leading to **hyperrenism**; often induces **angiodyplasia**; commonly see **heterologous elements** (glia, cartilage); CD34 +
HEPATOBLASTOMA

Clinical:
-Most common pediatric liver tumor, birth-5 years, 2:1 male predominance

Histology:
-Six histologic patterns: 1) Fetal: sheets of uniform fetal-type epithelial cells, smaller than normal hepatocytes, variable glycogen and lipid content gives “light and dark” low power look; 2) Embryonal: fetal-type cells admixed with pleomorphic small angulated cells with scant basophilic cytoplasm, mitoses common; 3) Macrotrabecular: trabeculae >10 cells thick, cell type variable; 4) Small-cell undifferentiated: small round blue cells; 5) Mixed epithelial and mesenchymal: can have osteoid, cartilage, rhabdoid differentiation; 6) Teratoid: variety of mature tissues present
-Extramedullary hematopoiesis common in fetal or embryonal patterns

Molecular/Genetic:
-5% of cases associated with congenital anomalies including horseshoe kidney, renal dysplasia, Meckel diverticulum, cleft palate, umbilical hernia, Beckwith-Wiedemann, trisomy 18, FAP, Gardner syndrome

ADRENAL CORTICAL CARCINOMA

Clinical:
-Bimodal age distribution (first two and 5th decades), may be associated with Cushing syndrome or sex steroid overproduction; usually malignant when >500 gm in children (>100 gm in adults)

Histology:
-Alveolar, trabecular, and solid proliferations of cells with vacuolated or eosinophilic cytoplasm, nuclei may be uniform or pleomorphic
-Can see extensive necrosis, globular eosinophilic inclusions
-Weiss Criteria: Nuclear grade; >5/50 HPF mits; atypical mits; clear or vacuolated cells <25% tumor; diffuse architecture; microscopic necrosis; venous invasion; sinusoidal invasion; capsular invasion (favor malignant if ≥3 features present)
-IHC +: A103, inhibinA, D11, calretinin, D240, synaptophysin, NSE

Molecular/Genetic:
-Occur in 1% of Li-Fraumeni syndrome patients (p53 mutations @ 17p13)

NEUROBLASTOMA

Clinical:
-Pediatric (<4 years) adrenal or abdominal masses; less commonly head and neck, mediastinal, pelvic; increased serum catecholamine + metabolites

Histology:
-Small round blue cells, thin fibrovascular cores separate into lobules, Homer Wright pseudorossettes
-Undifferentiated NB cases lack neuropil; Poorly differentiated NB have background neuropil, gananglionic differentiation rare; Differentiating NB have 5-50% of cells with ganglionic differentiation, Schwannian stromal formation at periphery... if >50% qualifies as Ganglioneuroblastoma
-IHC +: NSE, synapto/chromo, CD57 (leu-7), NCAM/CD56, NB84

Molecular/Genetic:
-Association with Beckwith-Wiedemann, Familial Adenomatous polyposis coli
-Undifferentiated NB cases lack neuropil; Poorly differentiated NB have background neuropil, gananglionic differentiation rare; Differentiating NB have 5-50% of cells with ganglionic differentiation, Schwannian stromal formation at periphery... if >50% qualifies as Ganglioneuroblastoma
-IHC +: NSE, synapto/chromo, CD57 (leu-7), NCAM/CD56, NB84

Molecular/Genetic:
-Association with Beckwith-Wiedemann, Familial Adenomatous polyposis coli

PANCREATOBLASTOMA

Clinical:
-Rare, presents in infancy or early childhood; elevated AFP

Histology:
-Islands, nests, and trabeculae of polygonal epithelial cells with central nucleoli, amphotrophic or eosinophilic cytoplasm, separated by variable amounts of cellular stroma; squamous nests are prominent; some cells form acinar and tubular-like structures, contain zymogen granules and may be mucin-positive
-Immunohistochemical profile highlights mixed acinar, endocrine, and ductal differentiation (CEA, EMA, NSE, synaptophysin, α1-antitrypsin, chymotrypsin, nuclear β-catenin)

Molecular/Genetic:
-Association with Beckwith-Wiedemann, Familial Adenomatous polyposis coli
FIBROUS DYSPLASIA

Clinical:
- Fibroosseous lesion in the jawbones, ribs, and femurs of patients <30
- On a spectrum with ossifying fibroma and cement-ossifying fibroma (COF);
  FD has less well-defined borders has a higher recurrence rate

Histology:
- Hypocellular proliferation of plump spindled cells with collagen
  production, irregularly shaped, often curvilinear trabeculae of woven bone
  (“C’s and S’s”)
- Osteoblastic rimming is rare (unlike in ossifying fibroma)

Molecular/Genetic:
- Albright Syndrome: multifocal fibrous dysplasia with skin pigmentation,
  endocrine hyperactivity, and precocious puberty
- Mazabraud Syndrome: fibrous dysplasia associated with intramuscular
  myxomas

OSSIFYING FIBROMA

Clinical:
- Benign jaw tumors, juvenile variant typically arises in maxilla and paranasal
  sinus walls; juvenile cases associated with more aggressive behavior

Histology:
- Islands and trabeculae of bone set in fibroblastic background
- May be identical to fibrous dysplasia; distinction is made on
  clinical/radiographic grounds (OF=circumscribed mass, FD=indistinct)
- Psammomatoid variant contains innumerable acellular to sparsely cellular
  mineralized deposits known as “ossicles,” may fuse to form trabeculae

Molecular/Genetic:
- Multiple tumors may be seen in hereditary hyperparathyroid-jaw tumor
  syndrome, mutation in HRPT2 on chromosome 1q encoding parafibromin

MECKEL DIVERTICULUM

Clinical:
- Most common intestinal congenital anomaly (~2% of general population)
- Occasionally leads to symptoms including obstruction, hemorrhagic ulcer,
  perforation, severe duodenitis
- Outpouching of antimesenteric border of terminal ileum, ~20 cm from
  ileocecal valve
- Represents persistence of the omphalomesenteric duct

Histology:
- Majority (50-70%) of cases show only small intestinal mucosal lining;
  remaining cases also have ectopic gastric and/or pancreatic tissue

PEUTZ-JEGHER POLYP

Clinical:
- Most often identified in patients with Peutz-Jeghers Syndrome although
  solitary lesions may be seen without syndromic association

Histology:
- Hamartomatous polyps with normal glandular epithelium residing on
  branching smooth muscle framework (Christmas tree appearance)
- Adenomatous and carcinomatous transformation may be seen (6-12%)

Molecular/Genetic:
- PJS is an autosomal dominant (75%) or sporadic (25%) disorder
  characterized by PJ polyps and mucocutaneous pigmentation
- Criteria for syndrome=a)≥ 3 PJ polyps; b) any # PJ polyps with family history;
  c) characteristic mucocutaneous pigmentation with family history d)
  characteristic mucocutaneous pigmentation and PJ polyps
- Patients also prone to ovarian sex cord tumor with annular tubules (SCTAT),
  adenoma malinum, testicular sertoli cell tumors
**CONGENITAL CYSTIC ADENOMATOID MALFORMATION**

*Clinical:*  
-Congenital lung disorder in which lobe is partially or entirely replaced by non-functioning cystic tissue  
-May be diagnosed on prenatal ultrasound; associated with polyhydramnios; leads to hydrops fetalis in 40% of cases  

*Histology:*  
-Type I: large (>2 cm) multiloculated cysts  
-Type II: smaller uniform cysts, solid regions  
-Type III: “adenomatoid” type, grossly solid rather than cystic, microscopically cyst-like spaces communicate with the surrounding parenchyma

**SEMINOMA**

*Clinical:*  
-Pure forms account for 50% of all testicular GCT; average age 40 (older than other testicular GCT)  
-Even pure seminoma may have elevated hCG due to trophoblastic elements; AFP should not be elevated  

*Histology:*  
-Diffuse sheeted, lobular, or rarely tubular proliferation of cells with clear to pale pink cytoplasm, central often squared nuclei, 1-2 central nucleoli, and well-defined cell borders; fibrous septa are prominent; dense lymphocytic infiltrates; ITGCN usually present  
-20% have trophoblasts, no impact on diagnosis  
-Most contain glycogen, stain with PAS  
-Immunostain for c-kit, PLAP, SALL-4, Oct3/4; CK8, CK18, NEGATIVE for CD30 and EMA; other CKs are limited

**TESTICULAR CHORIOCARCINOMA**

*Clinical:*  
-Pure forms are rare (0.3% of testicular GCT); a component is present in 10-20% of all mixed GCT; patients usually 2nd-3rd decade, often present with hemoptysis, GI bleeding, neurologic abnormalities due to metastases; can have gynecomastia, thyrotoxicosis secondary to hCG effects; respond well to chemotherapy  

*Histology:*  
-Proliferation of malignant trophoblastic cells with central hemorrhage and necrosis surrounded by a 2 cell population: 1) cytotrophoblasts and intermediate trophoblasts (mononuclear cells with clear cytoplasm and mild-moderate nuclear pleomorphism) and 2) syncytiotrophoblasts (multinucleated cells with abundant cytoplasm, often with intracytoplasmic lacunae containing erythrocytes)  
-Immunostain with hCG, mainly in syncytiotrophoblast cells, PLAP and EMA often positive, CEA positive in 25%

**TESTICULAR YOLK SAC TUMOR**

*Clinical:*  
-Pure form is most common GCT in prepubertal children, most common in toddlers with a range of 3 months to 8 years; in older patients occurs as a component of a mixed germ cell tumor; almost all have elevated AFP  

*Histology:*  
-Wide array of patterns: reticular (most common), macrocystic, papillary, solid, glandular-alveolar, mxyomatous, sarcomatoid, polyvesicular vitelline, hepatoid, paretial, endodermal sinus  
-Hyaline globules are common (PAS+, diastase-resistant, AFP negative)  
-Schiller-Duval (“glomeruloid”) bodies are seen in endodermal sinus pattern, consist of central vessel in core of mesenchyme lined by tumor cells and set in a cystic space  
-Immunostain with Glypican-3, SALL-4; AFP is patchy, not very useful, PLAP often positive but is not reliable; EMA negative
TESTICULAR EMBRYONAL CARCINOMA

Clinical:
- Pure form accounts for 10% of testicular GCT; a component is present in the majority of mixed GCT; 66% have metastases at diagnosis; usually do NOT have AFP elevation, LDH and PLAP may be increased

Histology:
- Large columnar to cuboidal cells often with dark, smudged appearance, ill-defined cell borders, amphophilic to lightly basophilic cytoplasm; may be arranged in papillae; prominent eosinophilic, coagulative necrosis
- ITGCN is common
- Immunostain for CD30, SALL-4, OCT3/4, CKs (unlike seminoma, not just CK8 and CK18), PLAP (patchy); negative for EMA, AFP is positive in a minority