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

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

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

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**

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

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

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 **mucicarimine**/**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

Histiology:

-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

Histiology:

-"**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

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, microcystic, macrocystic, polyvesicular vitelline, endometrioid-like, solid, papillary, adenofibromatous

-**Schiller-Duval Bodies** (papillae w/ central core containing vessel)

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**

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 **rossettes** 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

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**

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**

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 mesenychmal cells**

-Mitotic figures rare

-Overlying skin may show hyperplasia, duct dilatation, squamous metaplasia

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

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 pigmentary 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**

-**Rossettes 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, **cross-striations 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**

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 neosplasm

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

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/spindled 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

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

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

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 **angiodysplasia**; commonly see **heterologous elements** (glia, cartilage); CD34 +

PANCREATOBLASTOMA

Clinical:

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

Histology:

-**Islands, nests, and trabeculae of polygonal epithelial cells** with central nucleoli, amphophilic or eosinophilic cytoplasm, separated by variable amounts of **cellular stroma**; **squamoid 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**

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 fibrobascular 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:

-Prognostic**: *MYCN* gene amplification**, chromosome **1p loss, 17q gain**

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)

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 mucocutaenous 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 2^{nd}-3^{rd} 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 syncytiotrohoblast 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, parietal, 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