

PEDIATRIC PATHOLOGY WARM-UP ANSWERS

1. Answer A. Whenever you are faced with an ovarian tumor, it's critical that you keep these 4 categories in mind. By the end of your first year of training, you should be able to conjure a list of entities for each category: 1) **Germ cell tumors**: dysgerminoma, yolk sac tumor, embryonal carcinoma, mature teratoma, immature teratoma, choriocarcinoma; 2) **Sex cord stromal tumors**: Sertoli-Leydig cell tumors, granulosa cell tumors, fibroma, thecoma, the weird one known as "sex cord tumor with annular tubules" (SCTAT); 3) **Epithelial tumors**: Serous, clear cell, mucinous, endometrioid, and Brenner tumors. Of course don't forget **metastasis**; "Krukenberg tumors" from the GI tract are a favorite from this camp but don't forget breast, cervix, endometrium, and so forth. You can loosely "triage" items on your differential diagnosis based on patient age: germ cell tumors are the most common ovarian neoplasms in young children and adolescents, while stromal tumors have a peak incidence in early and middle adulthood and epithelial tumors are most common in middle-aged and older women. Just remember that these rules aren't written in stone: college students get serous ovarian carcinomas, nursing home residents get juvenile granulosa cell tumors, etc.

2. Answer E. This question brings up some important terminology for approaching pediatric pathology, mainly the broad categories of "**small round blue cell tumors**" and "**embryonic tumors**." Do you think that the term "small round blue cell tumor" (SRBCT) is equivalent to "embryonic tumor?" It's not, although there is significant overlap between the tumors encompassed in each category. First, know that SRBCT is not a diagnosis, it's a pattern. As the name indicates, SRBCT refers to tumors comprised of relatively uniform, primitive-appearing cells with round nuclei and little cytoplasm. It's worth noting that the cells often aren't all that small! A broad differential for a SRBCT might include neuroblastoma, medulloblastoma, retinoblastoma, Ewings/PNET, CLL/SLL, large cell lymphoma, desmoplastic small round cell tumor, embryonal rhabdomyosarcomas, mesenchymal chondrosarcoma, even neuroendocrine tumors like small cell lung carcinoma and Merkel cell carcinoma. "Embryonic tumors," on the other hand, recapitulate tissues seen in the developing embryo. While this often manifests in a SRBCT appearance, such as with neuroblastoma, medulloblastoma, retinoblastoma, and embryonal rhabdomyosarcoma, this is not always the case. Wilms tumor and hepatoblastoma, for instance, are embryonic tumors which only rarely show SRBCT histology. Pancreatoblastoma is an embryonic tumor which can have a heterogeneous morphology quite distinct from the SRBCT pattern! (See challenge question #43). While true "embryonic tumors" are largely restricted to young children (usually first few years of life), the SRBCT differential comes up across all age ranges.

3. False. Remember from your pediatric rotation in med school, “Children are NOT just little adults!” The same adage applies to their cancers! For instance, the Weiss Criteria are valuable for differentiating adrenal cortical adenomas from carcinomas in adults, but have no proven utility in identical tumors from kids. Pediatric gastrointestinal stromal tumors (GISTs) are quite different beasts from their adult counterparts. The list goes on!

4. Answer A. Although we might consider Ewing sarcoma if the lesion was unifocal and limited to the bone, the presence of an adrenal mass points us towards **neuroblastoma**. Metastasis at presentation is unfortunately quite common for neuroblastomas, so bone involvement should not surprise us. Also, this patient is on the young side for Ewing sarcoma (although it could certainly happen). Pheochromocytoma would come to mind for an adrenal tumor in an older patient, but is not a small round blue cell tumor and is metastatic in a minority of cases. Wilm’s tumors arise in the kidney, although when tumors are large it can sometimes be difficult to determine whether they originate in the kidney or the adrenal. Wilm’s tumor does not tend to metastasize to bones (it prefers the “3 L’s” ... see challenge questions #36-37 for details).

5. Answer A. If you went for Wilm’s tumor don’t beat yourself up, because this is the most common renal neoplasm in young children after 2 months of age. However, in the immediate neonatal period the most common neoplasm is **congenital mesoblastic nephroma**, a usually benign tumor of the renal mesenchyma. The answer choices are listed in order of decreasing frequency. Note that I specifically asked for the most common neoplasm, since the vast majority of renal masses in newborns are related to hydronephrosis or multicystic dysplasia.

PEDIATRIC PATHOLOGY CHALLENGE ANSWERS

1. Answer A. PAS-positive secretions are not a feature of monophasic synovial sarcoma (SS) although they can be seen in association with the glandular elements of biphasic synovial sarcoma. Although you might have guessed that monophasic SS by definition lacks epithelial elements, don’t be fooled! While not glaringly evident on H&E stain, small epithelioid clusters are often revealed by cytokeratin staining of monophasic SS. Both monophasic and biphasic variants may show a hemangiopericytoma-like vascular pattern, and indeed hemangiopericytoma/solitary fibrous tumor is on the differential diagnosis for monophasic cases. Microvilli are seen in both variants of SS. Finally, the X;18 translocation with SYT-SSSX1 or SYT-SSX2 fusion is specific for SS.

2. Answer C. **Calcified**. This is a tricky question, because while early investigations suggested that biphasic SS carries a better prognosis than its monophasic colleague, subsequent studies have shown that biphasic histology confers no independent prognosis significance. In addition,

early studies suggest SYT-SSX2 was favorable (more common in biphasic) but similarly in further studies shows no prognostic significance. However, patients with calcified SS (which are often biphasic) do have a more favorable outcome. The only other subtype with established prognostic significance is the “poorly-differentiated monophasic” variant, which is characterized by larger nuclei and more increased mitotic activity when compared to typical SS.

3. Answer B. A young adult patient with dermal/subcutaneous nodules, especially of the distal arm/wrist, and histology evocative of rheumatoid granulomas should prompt wildly aggressive red-flag waving in your brain. We’re worried about **epithelioid sarcoma**, which must be excluded before we blow these lesions off as inflammatory. Epithelioid sarcoma is **cytokeratin-positive** and **INI-negative**. Miss it at your—and the patient’s—peril. While work-up for infection and auto-immune processes would be warranted if CK is negative, in this setting exclusion of a malignant tumor is the first priority.

4. Answer A. The clinical and histologic description is consistent with a **glomus tumor**. These tumors are thought to be derived from modified smooth muscle cells known as pericytes. They are positive for **smooth muscle actin** and **muscle specific actin** but lack reactivity for desmin and endothelial cell markers.

5. Answer B. **Calcifying aponeurotic fibroma**. The description is classic for CAF: a painless hand or foot nodule occurring in a child and comprised of mature fibrous background with more primitive fibrosarcoma-like elements arranged in nodules with central calcification and/or chondroid. It’s important to note that infiltration by the mature fibrous component does not indicate malignancy.

6. Answer E. The location (head and neck) and histologic description are compatible with a diagnosis of **juvenile xanthogranuloma** with its classic (but not necessary) **Touton giant cells**. While positive for a variety of histiocytic/macrophage markers (CD68, lysozyme, HAM56, factor XIIIa), and the ubiquitous vimentin, JXGs should not stain with cytokeratins.

7. Answer D. **Alveolar rhabdomyosarcomas** tend to occur in the trunk and extremities; head and neck location is more common for the embryonal subtype. All other statements are true: when compared to embryonal tumors, alveolar rhabdomyosarcomas carry a worse prognosis and are more common in adolescents. Classic histology includes alveolar-like spaces however these may be absent in a solid variant. In solid cases, the diagnosis can be confirmed by the identification of multinucleated giant cells with wreathed nuclei; these should not be seen in embryonal rhabdomyosarcoma.

8. Answer E. **Embryonal rhabdomyosarcoma** cells are typically moderate to poorly differentiated, grow in sheets, and are typified by eosinophilic granular cytoplasm and eccentric nuclei. Cross striations are not commonly seen. Although **botryoid rhabdomyosarcomas** (which is a special subtype of embryonal rhabdomyosarcoma arising in association with lumens such as the bladder, genital tract, and conjunctiva) show the classic cambium layer underlying an epithelium and myxoid background, these features are not seen with other embryonal rhabdomyosarcomas. The prognosis is relatively favorable in children and worse in adolescents. While childhood cases most commonly occur in the head and neck, orbit, GU tract, and retroperitoneum, adolescents tend to get paratesticular and extremity tumors.

9. Answer A. The clinical, histologic, and immunohistochemical features fit with **desmoid fibrosis**. These tumors show a female predominance and most often arise in the abdomen, sometimes following surgery or parity. They are associated with the autosomal dominant (AD) **Gardeners Syndrome**, a variant of **Familial Adenomatous Polyposis** caused by APC gene mutations and characterized by myriad colonic adenomas, osteomas of the jaw and other locations, benign cutaneous tumors, adrenal adenomas, benign hypertrophy of retinal pigment epithelium, and unerupted teeth. Unlike patients with Peutz-Jeghers syndrome, who develop hamartomatous colorectal polyps, the polyps in Gardener's/FAP are conventional adenomas. Peutz-Jeghers patients are prone to mucocutaneous melanin spots and a variety of visceral malignancies. The endometrial carcinoma association is seen with Hereditary Non-Polyposis Colorectal Cancer (HNPCC)/Lynch Syndrome, an AD inherited polyposis syndrome attributable to germline defects in the mismatch repair genes MLH1, MSH2, MSH6, and PSM2. Sebaceous carcinomas are seen in Muir-Torre Syndrome, a variant/close relative of Lynch Syndrome. Cerebellar medulloblastomas and glioblastomas are associated with Turcot's Syndrome, another AD heritable polyposis syndrome which can be secondary to FAP or mismatch repair mutations.

10. Answer B. **Infantile fibrosarcoma** is characterized by the **t(12;15) translocation**, which results in ETV6-NTRK3 gene fusion. This translocation is also observed in **cellular congenital mesoblastic nephromas**. This translocation is notably absent in myofibromas, which are part of the differential diagnosis for fibrous lesions of infancy. While infantile fibrosarcomas are characterized by broad fascicles of uniform immature fibroblasts/myofibroblasts, myofibromas show a biphasic admixture of mature and immature myofibroblastic cells, often with prominent zonation.

11. Answer C. **Fibrous hamartomas of infancy** are triphasic proliferations of fibrous trabecular, disorganized mature fat, and scattered islands of immature mesenchymal cells. The adjacent

skin may show a variety of changes including hyperplasia, squamous metaplasia, and ductal dilatation. Mature cartilage is not a feature.

12. Answer A. The inclusions in **inclusion body fibromatosis** are perinuclear, eosinophilic, approximately the same size as erythrocytes, and stain for SMA and vimentin; they are not PAS positive. This entity classically arises on the dorsal aspect of the digits in young infants.

13. Answer D. The location and histologic description fits with **lobular capillary hemangioma**, also known as "**pyogenic granuloma**." This latter name is inappropriate because clonal evidence indicates that these are true neoplasms rather than reactive lesions. These tumors can occur at any age but are particularly common in pregnant women. Glomus tumors recapitulate the arterial component of a specialized AV-shunt found in the hands and feet ("Suquet-Hoyer canal"). Distinctive features of Kaposi's sarcoma include the "promontory sign" (new vascular channels forming cliff-like projections in pre-existing vessels), hyaline globules, plasma cells, and HHV8 positivity. Glomeruloid hemangiomas show vascular arrangements reminiscent of renal glomeruli and are associated with POEMs syndrome. Masson lesion or intravascular papillary endothelial hyperplasia occurs as a result of thrombosis within hemangiomas, hematomas, or dilated vessels; it demonstrates hyalinized papillary fronts lined by plump epithelial cells and can mimic angiosarcoma.

14. Answer B. **Plexiform fibrohistiocytic tumors** occur in young, often female patients and are characterized by dermal or subcutaneous nodules demarcated by a rim of fibrous tissue. The nodules are comprised of fibrohistiocytic cells and multinucleated giant cells with affiliated chronic inflammation. The distinctive "Touton" giant cells of JXGs are not a feature. While similar to giant cell tumors of tendon sheath, PFTs can be distinguished by their superficial location. Benign fibrous histiocytomas are dermal lesions occurring across all age groups comprised of small spindly cells with a frequently storiform arrangement; they lack multinucleated giant cells and tend to have an infiltrating, rather than fibrous, border.

15. Answer B. **Chondroblastomas** are benign* (*usually: lung mets may rarely occur) tumors commonly arising in the ends of long bones of patients in their second decade. The epicenter is usually in the epiphysis (important distinction from osteosarcoma), extension into metaphysis is common. The cytologic features described are classic, and "**chicken wire**" calcification is an important "buzz word." Most cases show chondroid differentiation.

16. Answer C. **Osteoblastoma** are rare, benign bone tumors with a male predominance. They most commonly involve the spine or diaphysis of long bone of patients in their second decade. They are histologically indistinguishable from **osteoid osteomas**; these two entities are separated by size (osteoblastoma: >1.5 cm). The clinical hallmark of osteoid osteoma is pain at

night relieved by aspirin; this is variably reported in osteblastomas. Osteoid osteomas are also less apt to involve the spine than their larger counterparts. Osteoblastomas show irregular spicules of mineralized bone and osteoid which are lined by osteoblasts; this is in contrast to fibrous dysplasia, which lacks osteoblastic rimming.

17. Answer D. **Non-ossifying fibromas (metaphyseal fibrous defects)** are most often identified in males in their second decade. They are usually incidental and are likely not true neoplasms. X-ray reveals lucent, elongated cortical or cortical and medullary defects with scalloped edges. Histology demonstrates a storiform proliferation of spindled cells with admixed benign giant cells. Mitotic figures may be numerous.

18. Answer A. **Osteosarcoma** most commonly arises in the long bones of adolescent males. The question describes the classic imaging finding of Codman triangle. Proximal and distal margins are usually well defined because the epiphyseal plate acts as a barrier. The tumor described is a conventional osteosarcoma, which are defined as high grade spindle cell neoplasms producing osteoid matrix. Conventional osteosarcoma can be further subdivided into osteoblastic, fibroblastic, and chondroblastic types, based on the predominant matrix.

19. Answer B. The tumor described is **fibrous dysplasia**, bone-forming bland spindle cell lesion which most often occurs in the jawbones, ribs, and femurs of children/adolescents. It is similar to ossifying fibroma but lacks a well-defined border. The osteoid does NOT show osteoblastic rimming. Fibrous dysplasia is associated with **Albright Syndrome**, which also includes skin pigmentation, endocrine hyperactivity, and precocious puberty. This syndrome was brought into the public eye by Haitian teenager Marlie Casseus, who underwent multiple surgeries to remove majorly disfiguring facial fibrous dysplasia... Google her if you want an image to stick in your mind. Gardner's syndrome is a variant of Familial Adenomatous Polyposis associated jaw osteomas. Cowden Syndrome is an autosomal dominant disorder caused by PTEN mutations which leads to hamartomatous lesions and predisposes to a variety of malignancies including breast, colon, thyroid, and uterus. Carney Complex (LAMB or NAME syndrome) includes lentiginos, blue nevi, cardiac myxomas, endocrine tumors, and large cell calcifying sertoli tumors. Do not confuse Carney Complex with Carney Triad, which consists of GIST, pulmonary chondroma, and extra-adrenal paraganglioma.

20. Answer D. Although typically indolent, **dermatofibrosarcoma protuberans** metastasizes in a small minority (~3%) of cases, generally associated with fibrosarcomatous transformation. It is typically a tumor of adults and is rare in children. The t(17;22) translocation is well-described and is shared with **giant cell fibroblastoma**, a related pediatric tumor. Histology shows a classic

storiform or “cartwheel” configuration of spindled cells and dermal infiltration is expected. Strong CD34 staining is the immunohistochemical hallmark. **Bednar tumors** are pigmented variants which show scattered dendritic melanocytes; differentiation from melanoma is clinically critical given the “intermediate” malignancy of DFSP as opposed to the more reliably aggressive course of melanoma.

21. Answer C. **Nodular tenosynovitis** most commonly arises in the hands and recurs in about one fifth of cases. On histology, the tumor is cellular with a component of benign multinucleated giant cells, abundant inflammatory cells, and hemosiderin deposits. However, florid papillary synovitis is not seen; rather, this is a feature of the related lesion **pigmented villonodular synovitis**. When compared to nodular tenosynovitis, PVNS also differs in localization (ankle and knee) and behavior (much more locally aggressive). Both lesions are encompassed under the term **giant cell tumor of tendon sheath** and both have been shown to have the COL6A3-CSF1 gene fusion.

22. Answer A. The clinical and histologic features are those of **fibroma of tendon sheath**, although presentation in a younger patient is somewhat uncommon (usually age 30-50). Some authors postulate that these represent burnt out nodular tenosynovitis/giant cell tumor of tendon sheath, so if you guessed “B” perhaps you’re not entirely incorrect. Inclusion body fibromatosis is seen in infants (infantile digital fibroma) and bear pathognomonic SMA-positive inclusions while calcifying aponeurotic fibromas are seen in young children and are characterized by fibrous tissue surrounding central chondroid/calcification.

23. Answer B. The histologic description fits with a **dermatofibroma**, which classically shows a dermal proliferation of bland spindled cells with admixed collagen bundles. “Lens-shaped” is a good buzz-word to remember for dermatofibroma. All the listed variants exist, but the combination of macrophages, hemorrhage, and Touton-like giant cells are associated with the **lipidized** variant.

24. Answer B. **Schiller-Duval bodies** are a classic (but often not encountered!) finding with **yolk sac tumors** and consist of tumoral papillae with a central core bearing a vessel. Choice A describes Cal-Exner bodies of granulosa cell tumors. Choice C describes psammoma bodies, common in a variety of papilla-forming tumors (ovarian, thyroid, etc) and thought to represent infarcted papillary tips. Choice D refers to Verocay bodies, classic in Schwannian tumors. Choice E refers to Homer-Wright rosettes, seen in primitive neural tumors. HW rosettes should

really be called “pseudorosettes” because true rosettes have an empty lumen (e.g. the Flexner-Wintersteiner rosettes of retinoblastoma).

25. Answer E. The most common pattern of yolk sac tumors is **reticular**, characterized by a loose meshwork of spaces lined by primitive tumor cells with clear cytoplasm. Usually some component of this pattern is present, even if other morphologies predominate. Other common patterns include the polyvesicular vitelline pattern, which has cysts lined by tumor cells and separated by dense stroma, and the hepatoid pattern, which resembles hepatocellular carcinoma. Nonspecific patterns including solid, papillary, and adenofibromatous may also be present.

26. Answer: False. Isolated syncytiotrophoblastic giant cells may be seen in a variety of germ cell tumors in males and females and do not independently indicate the presence of a choriocarcinoma component. Not surprisingly, these cells can be associated with elevated hCG, so don't assume that high hCG suggests choriocarcinoma either.

27. Answer C. A diagnosis of **choriocarcinoma** requires a biphasic proliferation of cytotrophoblasts and syncytiotrophoblasts. Other germ cell tumors frequently show isolated syncytiotrophoblasts but do not necessarily contain choriocarcinoma. The other statements are true.

28. Answer: False. **Peritoneal gliomatosis** consists of implants of mature glial tissue, as opposed to the immature neuroectodermal elements seen in the immature teratoma itself. Although these implants may continue to grow after removal of primary immature tumor (**growing teratoma syndrome**) they do not display aggressive behavior.

29. Answer D. The histologic description, as well as the LDH elevations, are classic for **dysgerminoma**. This tumor is histologically identical to **seminoma** of the testes. Scattered syncytiotrophoblasts are common findings without prognostic impact, although they may result in beta-HCG elevations.

30. Answers E & F. **Juvenile granulosa cell tumors** are, not surprisingly, most common in children but can occur at any age and are occasionally seen in older women; the histology, not the age, defines the tumor. They usually present at stage 1. Histology shows prominent, variably sized follicles containing mucicarmine-positive secretions. Unlike conventional

granulosa cell tumors, the nuclei can be quite atypical and “coffee bean”-like nuclear grooves are not a common feature.

31. Answer C. The histologic description fits a **Sertoli-Leydig cell tumor**, which is supported by the clinical evidence of virilization. The Sertoli element may form tubules, as is described in this relatively well-differentiated case, but may also be poorly differentiated without appreciable tubule formation. Crystals of Reinke are only rarely identified and are by no means necessary for diagnosis. Heterologous elements are occasionally encountered and are most often mucinous.

32. Answer C or G (it’s complicated, see below). The histologic description could apply to any small round blue cell tumor, but if it’s primary to the bone it’s **Ewing sarcoma**. Intersecting fibrous bands are often striking. Like PNETs, these tumors show **EWS-FLI1 fusion**, most commonly via **t(11;22)** but also through **t(7;22)** or **t(21;22)**. These tumors are positive for **PAS with diastase sensitivity**, indicating the presence of **glycogen**. **CD99** is also reliably positive. Interestingly, **intermediate filaments** can be seen on electron microscopy, which speaks to the pluripotency of these primitive cells. According to the books, we would not expect to see Homer Wright pseudorosettes (choice C), as these are an indicator of neural differentiation and point towards PNET, HOWEVER recent consensus among pediatric pathologists contends that this distinction is not diagnostically tenable and that HW pseudorosettes may indeed be seen in traditional ES cases.

33. Answer B. **Desmoplastic small round cell tumors** display dual cytokeratin and desmin staining as well as frequent positivity for WT1, EMA, NSA, and vimentin. Fetal mesothelium shows a similar immunophenotype, prompting the theory that these tumors could be regarded as “mesothelioblastomas.” Although DSRCT do harbor a t(11;22) translocation, this is not the exact same translocation that is seen in Ewing/PNET.

34. Answer B. This MKI is not independently suggestive of unfavorable histology.

Favorable histology group includes the following:

- Patients of any age with stroma-rich tumors without a nodular pattern
- Patients younger than 18 months with stroma-poor tumors, an MKI of less than 200/5000 (200 karyorrhectic cells per 5000 cells scanned), and differentiated or undifferentiated neuroblasts
- Patients younger than 60 months with stroma-poor tumors, an MKI of less than 100/5000, and well-differentiated tumor cells

Unfavorable histology group includes the following:

- Patients of any age with stroma-rich tumors and a nodular pattern

- Patients of any age with stroma-poor tumors, undifferentiated or differentiated neuroblasts, and an MKI more than 200/5000
- Patients older than 18 months with stroma-poor tumors, undifferentiated neuroblasts, and an MKI more than 100/5000
- Patients older than 18 months with stroma-poor tumors, differentiated neuroblasts, and an MKI of 100-200/5000
- Patients older than 60 months stroma-poor, differentiated neuroblasts, and an MKI less than 100

35. Answer B. This (rather confusing) question gets at some of the important issues surrounding prognosis for neuroblastoma patients. For details, see the table below, but the take home points are as follows: 1) **Old age and metastases are bad and trump all else.** Once a patient with metastases is over 18 month old, he is at high risk irrespective of histology, grade, and molecular features. 2) **MYCN amplification is bad** and is generally associated with high risk, even in young patients without metastasis. There are exceptions for some organ-confined tumors with a predominant Schwannian stromal component (see table). 5) **11q aberrations** are bad, but are not bad enough to bump a patient with non-metastatic disease out of the intermediate risk group. 4) **Hyperdiploidy is good**, and in the case of a <18 month old with metastatic tumor improves prognosis to low risk. However, its impact would not be sufficient to “rescue” prognosis for an older child.

INRG Stage	Age (months)	Histologic Category	Grade Differentiation	MYCN	11q aberration	Ploidy	Pretreatment Risk Group
L1/L2	Any	GN maturing; GNB intermixed	Any	Any	Any	Any	A: Very Low
L1	Any	Any, except GN maturing or GNB intermixed	Any	n/amp	Any	Any	B: Very low
				Amp	Any	Any	K: High
L2	<18	Any except GN maturing or GNB intermixed	Any	n/amp	No	Any	D: Low
					Yes	Any	G: Intermediate
	≥18	GNB nodular; neuroblastoma	Differentiating	n/amp	No	Any	E: Low
					Yes		Any
		Poorly differentiated or undifferentiated	n/amp	Any			
			Any	Amp	Any	Any	N: High
M	<18	Any	Any	n/amp	Any	Hyper-diploid	F: Low
	<12	Any	Any	n/amp	Any	Diploid	I: Intermediate
	12 to < 18	Any	Any	n/amp	Any	Diploid	J: Intermediate
	< 18	Any	Any	Amp	Any	Any	O: High
	≥ 18	Any	Any	Any	Any	Any	P: High
MS	<18	Any	Any	n/amp	No	Any	C: Very Low
					Yes	Any	Q: High
					Amp	Any	R: High

36. Answer B. This question describes **clear cell sarcoma of kidney**, formerly known as “bone metastasizing renal tumor of childhood.” Not surprisingly, it likes to go to bone and is often widely metastatic at presentation. Key features low power features include a pale blue tumor with scalloped borders and a thick capsule. Cytology is as described; note that

mucopolysaccharide vacuoles are a distinct feature. Multiple variant patterns (epithelioid, spindled, myxoid, etc.) exist which means that this tumor can mimic—and be mimicked by—a variety of other neoplasms. Consider it for any tumor in a young child (peak age: 2-3) but remember that it's quite rare.

37. Answers C and D. **Wilms tumors** usually occur in children aged 2-5 and are most commonly triphasic with blastemal, stromal, and epithelial contributions, although mono and biphasic cases also occur. Secretion of Epo, renin, VWf, and NSE may occur. Identification of anaplasia is critical because it is the single criterion for unfavorable histology. Anaplasia is present in ~5% of tumors and correlates with p53 expression. Loss of heterozygosity at 1p and 16q are also indicative of worse prognosis. Nephrogenic rests do not indicate unfavorable histology, but do correlate with increased risk of bilaterality. Metastases are to the 3 L's: Liver, Lung, and regional Lymph nodes.

38. Answer E. Based on the patient age (infant) and concurrent posterior fossa mass, this baby probably has a rhabdoid tumor. These are associated with posterior fossa AT/RTs in 15% of cases. The hypercalcemia is related to parathyroid hormone secretion by the tumor. Cytologically, these tumors are comprised of large rounded or polygonal cells with plenty of cytoplasm and prominent nucleoli. Cytoplasmic inclusions are useful for diagnosis and contain intermediate filaments on EM. Loss of INI1 expression can be demonstrated by IHC and is due to defects in chromosome 22.

39. Answer C. This question describes **metanephric stromal tumor**, which (as with metanephric adenofibroma and metanephric adenoma) is thought to be a hyperdifferentiated form of Wilms tumor. They are characterized by subtly infiltrative spindled cells bearing thin, hyperchromatic nuclei and thin cytoplasmic extensions. They are intimately admixed with native renal elements, sometimes eliciting juxtaglomerular cell hyperplasia in entrapped glomeruli. Angiodysplasia and heterologous elements may be present.

40. Answer C. Differentiating **adrenal cortical carcinoma** from adrenal cortical adenomas can be extremely difficult, especially in children. In adults size over 100 gm supports malignancy but malignant tumors in children are usually >500 gms. According to the Weiss criteria for adult tumors, other features supportive of malignancy include high nuclear grade, >5/50 HPF mitoses, atypical mitoses, diffuse architecture, microscopic necrosis, venous and/or sinusoidal invasion, capsular infiltration, and <25% clear or vacuolated cells. **HOWEVER**, these criteria have yet to be proven useful in pediatric cases. Tumors tend to be positive for calretinin, inhibinA, A103, D11, and D240 and can also show staining with synaptophysin and NSE. Rare

cases (1%) are associated with Li-Fraumeni syndrome. Both benign and malignant tumors may be hormonally active leading to symptoms such as virilization.

41. Answer A. The question describes dermal involvement by **Langerhans cell histiocytosis**. Letterer-Siwe disease refers to multifocal skin (+/- systemic) involvement and occurs in babies under age 2; the prognosis is very poor. Hand-Schüller-Christian disease typically affects children is the triad of exophthalmos, bony lytic lesions, and diabetes insipidus. “Eosinophilic granuloma” (out-of-date misnomer but it still comes up) refers to bone-limited disease which typically occurs in adults. “Histiocytosis X” is another defunct term referring to a type of pulmonary interstitial disease which arises in smokers and shows regression with smoking cessation.

42. Answer A. The **fetal pattern of hepatoblastoma** shows uniform cells which are smaller than normal hepatocytes. All other statements are true. Other patterns include small cell undifferentiated (small round blue cells), mixed epithelial and mesenchymal (shows osteoid, cartilage, and/or rhabdoid differentiation), and teratoid (variety of mature tissues present).

43. Answer F. A primary pancreatic tumor in an infant with **Beckwith-Wiedemann** is likely to be **pancreatoblastoma**. They are also associated with **Familial Adenomatous Polyposis**. All of the listed histologic/immunohistochemical features could be seen: these tumors have a distinctive appearance which includes polygonal epithelial tumor cells arranged in islands, nests, and trabeculae and set in a cellular stroma. The epithelial cells bear amphophilic or eosinophilic cytoplasm and central nucleoli. Squamoid nests are an eye-catching feature. Acinar differentiation may be present with demonstrable zymogen granules. The immunophenotype highlights the mixed acinar, endocrine, and ductal differentiation with positive stains including CEA, EMA, NSE, synaptophysin, alpha1-antitrypsin, chymotrypsin, and nuclear beta-catenin.

44. Answer E. This patient has **anaplastic large cell lymphoma (ALCL)**. Primary nodal disease is most common in children and adolescents. Histology shows pleomorphic large lymphocytes with abundant cytoplasm and frequent mitoses. The constituent cells are positive for CD30. Scattered cells showing kidney or donut-shaped nuclei with an eosinophilic region adjacent to the nucleus are known as “Hallmark cells.” 60% of cases show at least cytoplasmic staining for ALK1. The combination of cytoplasmic and nuclear staining is typical of the classic **t(2;5)(p23;q35)** translocation which results in NPM-ALK fusion; this is present in 75% of all ALK1-positive cases. Cytoplasmic staining in the absence of nuclear staining suggests a variant translocation. The presence of a t(2;5) translocation correlates with improved survival.

45. D. The classic translocation in **Burkitt lymphoma** is **t(8;14)(q24;32)** which places the **myc** gene next to the **Ig heavy chain** gene. This translocation is present in about 80% of Burkitt lymphomas, with the remaining cases showing variants often involving 2p11 and 22q11. The classic Burkitt translocation may also be seen in other entities such as diffuse large B-cell lymphomas.

46. Answer D. Pure **yolk sac tumor** is the **most common GCT in prepubertal patients**, especially ones this young. After age 8 yolk sac is a common contribution in mixed tumors but is unlikely to occur in pure form. The other germ cell tumors listed would be more likely in adolescents and young adults.

47. Answer F. When compared to other testicular GCTs, **spermatocytic seminoma** is an outlier in many ways. It occurs in a much **older** patient population (40s-80s), which is why we wouldn't expect to see it in a sample from a pediatric surgeon. Unlike other GCT, intratubular germ cell neoplasia (**ITGCN**) is **not identified**. It is characterized by **3 cell types**: small cells with high N:C ratios, medium-sized cells with prominent nucleoli, and large cells. The fibrous septa and lymphocytic infiltrates typical of classic seminoma are notably absent.

48. Answer A. **Meckel Diverticula** are located close to the IC valve, but not that close! More like 20cm, or 2 feet as the "Rule of 2s" suggests. The other "2s" to remember are 2% of the population, 2 inches in length, 2% symptomatic, 2 years most common age of presentation, and 2x more common in boys.

49. Answer D. The **plasma cell variant** of **Castleman** does not typically demonstrate the classic "lollipop" lesions of the hyaline vascular type. The prominent plasma cells are generally polytypic, in contrast to plasmablasts in the plasmablastic variant which are usually IgM lambda-restricted and may form microlymphomas. Both the plasma and plasmablastic variants are usually multicentric and are associated with HHV8 with or without concurrent HIV infection.

50. Answer A. **Congenital cystic adenomatoid malformation** is a developmental abnormality of the lung which results in cyst production and non-functioning lung tissue. They are usually diagnosed by the first month of life and may be seen on prenatal ultrasounds. There are 4 types : Type I is defined by at least one large (2-10 cm) cysts with or without associated smaller cysts. Type II is comprised of uniform smaller (0.5-2 cm) cysts resembling bronchioles. Type III or "adenomatoid" cysts are grossly solid without identifiable cyst formation. Type IV refers to delicate, multicystic structures which may have some overlap with type 1 pleuropulmonary blastoma.