PathMD™: Board Review Letter

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Question 1

A 60-year-old female was found in the local woods by a dog walker. She was fully clothed, and there were no signs of trauma or foul play. At autopsy performed at Medical Examiner's office, lymphadenopathy involving hilar, mediastinal and retroperitoneal lymph nodes, hepatomegaly (3600 grams) and splenomegaly (1110 g) were identified. There were no distinct masses on gross examination of the liver, spleen or other internal organs. Several days later, the woman was identified by her daughter, who revealed the following information. Past medical history of the decedent was significant for squamous cell carcinoma of the face treated with radiation therapy. Two weeks ago she was hospitalized for evaluation of newly developed anemia. Upon physical examination, a markedly enlarged lymph node was found in her left armpit. The lymph node was removed, and shortly after the procedure the patient left the hospital against medical advice. Examination of the lymph node by H & E and immunohistochemistry at the local hospital established the diagnosis of anaplastic large cell lymphoma (ALCL). Histologic sections of the liver and spleen at autopsy revealed cells consistent with ALCL (see image of the liver on website).

All of the statements about the immunophenotype and genetics of this entity are true **EXCEPT**:

A. The majority of ALCL are positive for EMA
B. ALK staining is both cytoplasmic and nuclear
C. Tumor cells are strongly positive for CD25, CD30 and variably positive for CD45
D. Both ALK + and ALC - ALCL share the same cytogenetic abnormality
E. CD2, CD5 and CD4 are positive in significant proportion of cases

The correct answer is D. ALK- anaplastic large cell lymphoma is a CD30+ T-cell neoplasm, which is not reproducibly distinguishable on morphological grounds from ALCL, ALK+ but lacks anaplastic large cell lymphoma kinase (ALK) protein and specific cytogenetic abnormality. In the majority of ALCL, ALK+ cases have the t(2;5)/NPM-ALK translocation. The rest of the statements are correct.

References:

1. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Fourth Edition, pp. 312-319

Question 2

This anterior abdominal wall mass was an incidental autopsy finding in 48-year-old male alcoholic, who was found dead in his locked and secure apartment. Grossly, the mass was large, white and firm, filling the right abdomen (see photos). Microscopic images of the lesion are provided on the website.

Which statement about this entity is **FALSE**?

A. Postoperative radiation is frequently recommended
B. It is associated with Gardner syndrome
C. Beta-catenin nuclear positivity can be supportive of the diagnosis
D. It displays high mitotic activity
E. It is twice as common in females than in males

The correct answer is D. Mitoses are usually not identified or very rare in desmoid fibromatosis. This entity has a strong female predilection, and intra-abdominal and pelvic fibromatoses occur almost exclusively in women (answer E). In Gardner syndrome, fibromatoses commonly are mesenteric, and postoperative rate of recurrence is high (answer B). Other components of this syndrome are multiple colonic polyps and occasionally multiple osteomas. Beta-catenin nuclear positivity is observed in fibromatosis but it is not specific (answer C). Fibromatosis often recurs after initial excision, and postoperative radiation is frequently recommended (answer A).

References:
1. Sternberg's Diagnostic Surgical Pathology, 5th edition (August 24, 2009), vol.1, pp. 147-148

Question 3
An infant delivered by caesarean section at 31 weeks gestation died within an hour after birth despite active resuscitation. At autopsy, edema of the face and abdominal distension were noted. The thoracic cavity was filled by the pericardial sac distended by effusion and cardiomegaly. Massive hepatomegaly was noted. Microscopic examination of the majority of the internal organs revealed the following (see images). The results of a post delivery hemoglobin electrophoresis are provided on the website.

The underlying cause of this newborn condition is:

A. Four defective genes on chromosome 16
B. Trisomy 21
C. One abnormal gene on chromosome 11
D. Abnormal termination codon in α-gene on chromosome 16
E. Deletion of beta and delta genes on chromosome 11

The correct answer is A. Gross autopsy findings are consistent with hydrops fetalis associated with fetal anemia. Microscopic examination demonstrates extramedullary hematopoiesis. Alkaline hemoglobin electrophoresis displays total abscence of Hb A and Hb F. Fast-migrating hemoglobin Bart's is present. For boards purposes, it is useful to remember that hemoglobins J, Bart's, N, I, H migrate faster than A in the given order on cellulose acetate (alkaline) electrophoresis. On acid gel both F and Bart's co-migrate and are close to the cathode end. Hemoglobin Bart's hydrops fetalis (the most extreme form of alpha-thalassemia) is caused by loss of four α-genes on chromosome 16. In compensation, γ4 tetramers are produced. Their precipitation in utero results in marked anemia with subsequent development of high output cardiac failure. Trisomy 21 (answer B) can be associated with hydrops fetalis due to possible cardiac defects but it does not produce abnormalities on hemoglobin electrophoresis. One abnormal beta gene on chromosome 11 (answer C) is characteristic for beta-thalassemia minor. On hemoglobin electrophoresis, one sees high HbA2 (over 3.5%) and normal HbF. Hb Constant Spring (answer D) results from a mutation in the α gene stop codon, producing an abnormally long transcript that is unstable. In the heterozygote, the hemoglobins produced are: α-β (HbA), α^{cs}-β (HbCS), α-δ (HbA2), α^{cs}-δ (four bands are seen in the adult on cellulose acetate electrophoresis). In the newborn, α-γ (HbF), and α^{cs}-γ are also seen. Hereditary persistence of fetal hemoglobin (HPFH) results from a delayed switch from gamma to beta or delta chains. This can result from deletion of the beta and delta genes (answer E). In deletional forms of HPFH homozygotes have slightly microcytic, hypochromic red cells, but no anemia. Hb F is 100%; no Hb A or Hb A_2 is present. In the heterozygote, no hematologic abnormalities are found. Hb F is 15-30%, and Hb A_2 is 1-2.1%. Hb F is homogeneously distributed among the red cells (pancellular). This is in contrast to β- or δβ-thalassemia, in which the distribution is heterocellular.

References:
1. Quick Compendium of Clinical Pathology: 2nd Edition, Daniel D. Mais, Chapter 4: "Diseases of red blood cells"
2. Henry's clinical diagnosis and management by laboratory methods, 21 edition, chapter 31: "Erythrocytic disorders"

Question 4

An autopsy of a child with spina bifida revealed widening of the central canal of the spinal cord, hydrocephalus and myelomeningocele (see images on website).

Which statement about this condition is **FALSE**?

A. It shows pattern of elevated AFP, normal hCG, low uE in maternal serum
B. This condition is caused by incomplete neurulation of neuraxis at the end of the first 4 weeks of embryonic life
C. It has been associated with maternal diabetes and anticonvulsant therapy
D. It has specific pattern of inheritance
E. Treatment of expectant mothers reduces the risk of this condition in fetus

The correct answer is D. Spina bifida complicated by hydromyelia, hydrocephalus and myelomeningocele is an example of neural tube defect (NTD). NTDs are caused by incomplete neurulation of any point of neuraxis at the end of the first 4 weeks of embryonic life (answer B). Several environmental factors, including maternal diabetes and anticonvulsant therapy, have been identified (answer C). Treatment of expectant mothers with folate reduces the risk of NTD (answer E). Prenatal detection of NTD relies on screening by serum and amniotic chemistry and prenatal ultrasound (answer A). In spite of occasional occurrence of NTDs in trisomy 13 and 18, most data support a multifactorial cause.

References:
1. Neuropathology (a volume in the series foundation in diagnostic pathology) by Richard A. Prayson, pp.97-107
2. Quick Compendium of Clinical Pathology: 2nd Edition, Daniel D. Mais, Chapter 1: "Laboratory tests in pregnancy"

Question 5

A 44-year-old female with a past medical history of hepatitis B, C, rheumatoid arthritis and oxygen dependent emphysema was hospitalized for exacerbation of COPD. The patient had a history of heavy smoking (40 pack-years) since the age of 18 and of intravenous methylphenidate (Ritalin) and Percocet abuse for 4 years, 20 years previously. The hospital course was complicated by pneumonia, fungemia and subsequent death of respiratory failure. At autopsy, severe bilateral emphysema and extensive anthracosis of hilar lymph nodes were noted. Microscopic examination of the lungs by H & E and under polarized light revealed the following (see images on website).

The correct statement about this condition is:

A. The crystals are birefringent under polarized light
B. CT findings include large and irregular attenuated nodules ("ground glass") in the middle and upper part of the lung
C. The particles of the foreign substance usually exceed 10 μm
D. Lower-lobe panacinar emphysema is more common in methylphenidate abusers
E. The condition can progress to a fatal pulmonary disease years after discontinuation of drug use
F. All of the above is true

The correct answer is F – all of the above is true. This is an example of **pulmonary talcosis** due to intravenous abuse of crushed pills (in this case, Ritalin and Percocet). Talc, a hydrous magnesium silicate, is used as a lubricating and diluting substance in many oral medications. The talc crystals are filtered by the pulmonary vascular bed forming foreign body granulomas within the alveolar capillary walls and perivascular area. The talc particles deposited in the lungs following intravenous administration are larger than those observed for inhaled talc (10 μm vs. 5 μm). Progressive massive fibrosis secondary to intravenous talc injection has been described with particles larger than 15 μm. The early restrictive and obstructive features of talcosis due to intravenous use may progress to severe, sometimes fatal, pulmonary disease, even in patients who have discontinued use of the drug. Typical findings on computed tomography (CT) include large and irregular attenuated nodules ("ground glass") in the middle and upper part of the lung, which can evolve to large masses or massive consolidations. The presence of lower-lobe panacinar emphysematous processes is more common in methylphenidate abusers. Birefringent talc crystals can be identified under polarized light in tissue samples.

References:

1. Successful lung transplantation for talcosis secondary to intravenous abuse of oral drug, Shlomi D. at all, Int J Chron Obstruct Pulmon Dis. 2008 June; 3(2): 327–330.

Question 6

A 95-year-old female with the end stage of Alzheimer's disease was found dead in her apartment. Her relatives live in Canada and speak regularly with her by phone. The building manager checked on her when the family was unable to reach her for two days. Postmortem examination at the Medical Examiner's office revealed a cachectic elderly woman with external signs of dehydration. Vitreous fluid and blood samples were drawn. Which postmortem vitreous chemistry pattern is most characteristic for dehydration?

A	↑ vitreous Na^+	↑ vitreous Cl^-	→ vitreous K^+	↑ serum BUN	↑ serum creatinine
B	→ vitreous Na^+	→ vitreous Cl^-	→ vitreous K^+	↑ serum BUN	↑ serum creatinine
C	↓ vitreous Na^+	↓ vitreous Cl^-	↓ vitreous K^+	→ serum BUN	→ serum creatinine
D	↓ vitreous Na^+	↓ vitreous Cl^-	↑ vitreous K^+	→ serum BUN	→ serum creatinine

The correct answer is A. Vitreous sodium and chloride are very stable. Both closely reflect antemortem electrolyte status, and can be used in conjunction with BUN and K^+ to categorize the patient into one of several patterns. Sodium and chloride levels begin to decrease immediately after death, both at a rate of approximately 0.9 mEq/L/hour. Individual variation precludes their use in determining the postmortem interval. Serum and CSF potassium rise quite abruptly after death. Vitreous potassium rises more linearly after death and is probably the most reliable chemical test for postmortem interval. Normal vitreous K^+ is anything under 15 mEq/L. BUN and creatinine are remarkably stable after death. In addition to its value in

diagnosing renal insufficiency, mild nitrogen retention in conjunction with hypernatremia is useful to diagnose dehydration. Answer B is characteristic of uremia. Answer C reflects low salts status. Pattern in Answer D is seen in decomposition.

References:
1. Compendium of Clinical Pathology: 2nd Edition, Daniel D. Mais, Chapter 1: Postmortem chemistries.

Questions 7-9
This question consists of three parts.
A 20-year-old white male with a long standing history of epilepsy was found dead face down in his bedroom. The relatives of the deceased stated that his condition worsened recently. The seizures became more frequent and were poorly controlled despite adjustment of medications. An autopsy was performed at Medical Examiner's office. The external examination of the body revealed multiple, firm, brown, telangiectatic papules located in the nasolabial folds, chin, and cheeks (see gross image). The areas of thick leathery skin resembling an orange peel were found on the lower back and posterior neck. Examination of formalin-fixed brain revealed expanded, pale and firm gyri in both frontal and parietal lobes (see gross images on website).

Question 7
Based on the information provided, name gene product and corresponding chromosome responsible for the above findings.

A. Merlin, chromosome 22
B. Neurofibromin, chromosome 17
C. Hamartin, chromosome 9
D. INI protein, chromosome 22
E. Tuberin, chromosome 16
F. C and E
G. B and D

The correct answer is F (C and E). This patient displayed stigmata of tuberous sclerosis complex ("adenoma sebaceum", "ash leaf spots", Shagreen patches and cortical tubers). Past medical history of epilepsy is very characteristic of this condition. In fact, the most common cause of death in patients with tuberous sclerosis complex is status epilepticus or bronchopneumonia followed by renal failure. The TSC1 gene on chromosome 9q34 encodes a protein hamartin, and the TSC2 gene on chromosome 16p13.3 codes for tuberin. Both hamartin and tuberin show widespread expression in the brain and other organs affected in TSC. TSC follows an autosomal dominant pattern of inheritance. The name "merlin" (answer A) is an acronym for "Moesin-Ezrin-Radixin-Like Protein". In humans, it is a tumor suppressor protein involved in neurofibromatosis type II. The NF2 gene is located at chromosome 22q12. Neurofibromin (answer B) is a regulator of the *ras* signal transduction pathway. In addition to type 1 neurofibromatosis, mutations in neurofibromin can also lead to juvenile myelomonocytic leukemia. The NF1 gene is located on chromosome 17q11.2. Integrase interactor-1 (INI1) is a tumor supressor gene located at chromosome 22q11.2 (answer D). Deletion of INI1 leads to rhabdoid tumors predisposition syndrome, which is characterized by a markedly increased risk to develop atypical teratoid/rhabdoid tumour (AT/RT) of CNS, rhabdoid tumors of the kidneys and soft tissue. Loss of INI1 protein expression is demonstrated in neoplastic cell by immunohistochemistry.

Question 8
Sectioning of the formalin fixed brain also showed well-demarcated, multinodular masses of fleshy, gray–pink tissue in the wall of the lateral ventricles. Cut surface of the lesions displayed foci of calcification. Gross and microscopic images are provided on the website.

All the statements about this lesion are true **EXCEPT**:

A. It is the most common CNS neoplasm in patients with tuberous sclerosis complex
B. Considerable nuclear pleomorphism and increased mitotic activity denote adverse clinical course
C. It corresponds to WHO grade I
D. It typically arises in the wall of the lateral ventricles
E. Calcifications and signs of previous haemorrhage may be present

Correct answer is B. This is subependymal giant cell astrocytoma (SEGA), which is one of the major criteria for the diagnosis of TSC. SEGA may demonstrate increased mitotic activity. Considerable nuclear pleomorphism and multinucleated cells are frequent. However, these features do not appear to indicate an adverse clinical course. The rest of the answers are correct.

Question 9
What are other major manifestations of TS? (Choose ALL applicable):

A. Subungual fibromas
B. Cardiac rhabdomyomas
C. Optic nerve glioma
D. Large cell calcifying Sertoli cell tumor (LCCSCT)
E. Pulmonary lymphangioleiomyomatosis
F. Dysplastic gangliocytoma of the cerebellum
G. Epididymal cystadenoma
H. Renal angiomyolipomas

Correct answers are A, B, E and H. Note, that lymphangioleiomyomatosis and angiomyolipoma belong to the family of PECOmas. Subungual fibromas are also known as Koenen's tumor; they are present in 50% of tuberous sclerosis cases. Epididymal cystadenomas (answer G) are found in Von Hippel Lindau disease. Optic nerve glioma (answer C) is associated with NF1. Large cell calcifying Sertoli cell tumor (answer D) is associated with Peutz-Jeghers syndrome and is a component of Carney's complex. Dysplastic gangliocytoma of the cerebellum, also known as Lhermitte-Duclos disease, is pathognomonic of Cowden disease (mutation in PTEN on chromosome 10).

References:
1. WHO Classification of Tumours of the Central Nervous System, Fourth Edition; Louis, D.N., Ohgaki, H., Wiestler, O.D., Cavenee, W.K.; Chapter 13: Familial tumor syndromes.

Question 10

A 64-year-old white woman was found dead in bed by her husband. According to him, the deceased was a former drug user with a history of schizophrenia and depression. She was taking several prescribed medications including methadone. Recently, she was in her usual state of health and had no complaints. An autopsy performed at Medical Examiner's office revealed splenomegaly (760 grams) with prominent white pulp on sectioned surfaces (see gross image). No lymphadenopathy was noted, and the rest of the organs were grossly unremarkable. Microscopically, the splenic white pulp was expanded. Within the nodules, two populations of cells were present: numerous small cells and less frequent large cells (see microscopic photos on the website). By immunohistochemistry, the cells were CD20+, CD10+, BCL6+, BCL2+, CD5-, CD43- and CD 23-.

What is true about this entity?

A. In bone marrow, it localizes to the paratrabecular region
B. Strong BCL2 expression is very specific for this tumor
C. Translocation t(11;18) is seen in 90% of the cases
D. It is graded by counting the number of centrocytes
E. In 25%-35% of cases, transformation to DLBCL is seen
F. A and E

The correct answer is F (A and E). Follicular lymphoma (FL) can present with splenomegaly and minimal or absent lymphadenopathy. In such cases it is referred to as splenic follicular lymphoma. The morphology, immunophenotype and genetic features of extranodal FL appear to be similar to those of nodular FL. Expression of BCL2 is not unique for FL (answer B). BCL2 is expressed by most low grade and many high grade B-cell lymphomas. BCL2 is a useful marker to distinguish between reactive follicular hyperplasia and lymphoma. FL is graded by counting CENTROBLASTS, not centrocytes (answer D). Currently, grade 1 and 2 are lumped together in "low grade" category (0-15 centrocytes per hpf). t(14;18) is seen in 90% of FL (answer C). MALT lymphoma is characterised by t(11;18).

References:

1. 1. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Fourth Edition, pp. 220-226.
2. Splenic Follicular Lymphoma: Clinicopathologic Characteristics of a Series of 32 Cases, M Mollejo et all, Am. J. of Surg. Path, May 2009 - Volume 33 - Issue 5 - pp 730-738.

