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Clinical Vignettes for Second Year Pathology Education.

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ABSTRACT

Pathology is the fundamental basis for understanding physiology and disease mechanisms. At UCSD the pathology course is integrated into individual organ system blocks divided into lectures and laboratory activities led by pathologists. The current curriculum places emphasis on identifying and interpreting pathological features. A major hurdle in pathology education has been how to make the rather academic and scientific discipline clinically relevant for medical students. To introduce students to how pathology works in real-life in conjunction with other medical specialties, and to reinforce clinical relevance of pathological discoveries, especially for second year medical students who are about to take board exams and enter the wards, this project has generated many clinical vignettes based on the specimen slides students see under the microscope, featuring realistic diagnosis, disease course, and screening guidelines as well as some underlying molecular mechanisms when appropriate to complement pathological teachings.

BACKGROUND

Pathology curriculum at UCSD has been undergoing some major changes since its inception decades ago. As Dr. Katsumi Miyai, a longtime professor in the Department of Pathology who joined UCSD in 1970 and still teaches medical students, has always said, pathology is about "low power scope and higher power brain," meaning that a proper and complete understanding of pathophysiology is necessary to identify and interpret a specimen sample. Medical students learn about normal physiology in their first year of medical school, and are extensively trained in anatomy in their year-long anatomy laboratory. They also learn about how normal tissue structures present in histology laboratory. Students begin their pathology training starting their second year, when they are introduced to disease processes for the first time. The current pathology curriculum is not an independent block specific to pathology; instead, pathology is interspersed and integrated to individual organ blocks, meaning that a second-year medical student is continually learning about pathology throughout the year, which is more conducive to learning as it tightly ties a particular specimen to a particular disease entity.

The pathology course is divided into lectures and laboratory sessions. Lectures are given prior to start of laboratory sessions as an introduction to help students identify particular samples, and understand how pathophysiology manifests as such. In laboratory sessions students are taught how to use a microscope properly, and assigned a box containing prepared slides from different organs and diseases. Faculty instructors are always present during these laboratory sessions, and may give a small lecture before students start using their microscopes, and are always present to offer individualized help in using the right magnification, finding the right area, and explaining the pathologic features.

Pathology has been the cornerstone of medicine where disease processes are investigated, but unfortunately students have been showing decreasing interest in pathology, as indicated by dwindling attendance in the laboratory sessions throughout the years. One particular reason could be that UCSD has a fairly robust IT support, and many pathology slides are available online at MedPics. These online slides are excellent tools because they provide clear explanation with legends linked to each slide. To some students these online slides may make looking through an actual microscope anachronistic because online pictures often appear much more clear and representative than old slides from the boxes, whose staining and colors may have faded over the years. Efforts have been put into increase attendance, such as an in-class quiz at the end of each session asking students to identify particular specimens projected on to the whiteboard, and a cumulative pathology grade tracking a student's performance on these quizzes. However, there are other ways to make pathology more relevant to a student's education.

How a specimen appears under a microscope may not be enough to make a diagnosis on its own. A patient's clinical history, physical exams, and other laboratory tests are all necessary in conjunction with pathological findings to make the exact diagnosis. Up till now, the pathology course focused on identifying and interpreting particular structures. Because students in the second year are beginning to learn about case presentations as in Problem Based Learning classes, and about formulating a differential diagnosis based on clinical history and physical examination from

such a case, it is befitting for pathology to incorporate clinical vignettes along with the pathology slides. This approach would make pathology much more clinically relevant and engage students in "high power brain." Therefore the goal of this Independent Study Project is to generate clinical vignettes appropriate to each system block and incorporate them into pathology slides to educate students how pathology integrates with other patient information in formulating correct diagnoses, as happens in a real hospital setting.

RESULTS

The clinical vignettes are written to corresponding glass slides that students examine under the microscope. Usually the cases are presented without revealing the diagnosis, but providing enough clinical information to point to a certain diagnosis or differential diagnoses. In addition to illustrating pertinent pathological features of the slide, some general clinical suggestions regarding management or diagnosis are often interwoven to the vignettes.

In order to stimulate the students to think critically starting from the slides under their microscopes, the cases are written in question and answer format. Each case has multiple questions with answers revealed at the end of the laboratory session. Students are either provided printed handouts or have electronic access to these questions prior to each session.

Second year medical curriculum is divided into organ systems. Cases are written for cardiovascular, pulmonary, gastroenterology, endocrine and reproductive, and oncology blocks. Neurology and renal blocks have their own integrated pathology curriculum and no new vignettes were written. The vignettes are written with sources from pathology textbooks such as Robbins & Cotran *Pathologic Basis of Disease,* UCSD pathology MedPics for pathological descriptions, and Uptodate website especially for clinical presentations and current screening or treatment guidelines. To maintain accuracy of information, the cases were proofread with Dr. Tipps and other course directors prior to incorporation into the course.

The cases are written not only to explain pathological features or pathophysiology, but also to offer a connection to differential diagnosis and management. For example, the case for colon adenocarcinoma starts with a senior patient presenting with fatigue and subsequent labs showing anemia. The first question is actually management, namely asking what is the next step. In here the students learn that anytime an elderly patient presents with fatigue and anemia, iron panel, fecal occult blood test, and/or colonoscopy are warranted because GI bleeding from sources such as colon cancer is a common cause of iron-deficiency anemia especially among the elderly. Then the case goes into guidelines for screening for colon cancer, and finally pathophysiology of a polyp transforming into adenocarcinoma, and associated pathological features on the slide. As this case demonstrates, pathology is not just about diagnosis and what is under the microscope, but also about processes preceding it such as symptom presentation, screening, management, and pathophysiology. From the March 2015 Pathology Thread SET meeting, "[s]tudents found it very valuable when clinical cases are associated with each slide/each block." The cases can be found online in UCSD MedPortal website, but are reproduced in the next section. Due to time constraints, the vignettes may be modified to fit the time available in the actual laboratory sessions.

CLINICAL VIGNETTES

Block 1: Principles of Clinical Oncology

1) Reversible damage: non-alcoholic fatty liver disease (slide: steatosis)

A 55 year old Caucasian male presents for routine checkup. He has no current complaints besides increased anxiety at work due to economic downturn. PMH is noted for uncontrolled hypertension and hyperlipidemia, and obstructive sleep apnea. FH includes diabetes in his father and brother, and early heart attack in his maternal grandfather. Patient does not smoke, drink, or use illegal drugs. On exam his vitals were T 98.5°F, HR 88 bpm, 145/88 mmHg, RR 20, and 95% sat on RA. His body habitus is described as "apple-shaped" and his BMI is 36 kg/m^2. PE was grossly normal. Labs revealed normal chemistries and blood counts, but fasting glucose 121, HbA1c 6.3%, TG 150, total cholesterol of 260, HDL 10, LDL 240, and TG of 228. A plan was made to help the patient take his medication on-time and encourage him to exercise and cut down alcohol.

Q1: What does this patient have? What are criteria for metabolic syndrome?
A1: Three or more of the following:
Glucose: fasting glucose ≥ 100 mg/dL
HDL: below 40 in men, ≤ 50 in women
TG: TG ≥ 150
Central obesity: waist circumference ≥ 40 inches in man, and ≥ 35 inches in women.
Blood pressure: BP ≥130/85.

Q2: The patient also has mildly elevated liver enzymes with AST and ALT in 150s range. His viral panels are normal. What does he have, and what is worrisome in this condition?
A2: Elevation of liver enzymes in a patient with metabolic syndrome who does not drink alcohol and otherwise has no history of hepatitis is likely due to non-alcoholic fatty liver disease, or NAFLD. NAFLD is generally a reversible condition, but if left untreated can progress to non-alcoholic steatohepatitis, or NASH.

Q3: NAFLD was likely in this patient, but NASH or cirrhosis are not definitively ruled out. Therefore he underwent a liver biopsy to assess his condition. How are NAFLD and NASH different and what are expected to be shown by biopsy?
A3: NAFLD is a spectrum of non-alcoholic diseases subdivided into NAFL and NASH. In NAFL, there is no evidence of inflammation, although steatosis is present. NAFL may progress to NASH, which has inflammation and may appear indistinguishable from alcoholic steatohepatitis. NASH can progress to fibrosis or cirrhosis if left untreated. Fibrosis has a distinctive "chicken wire" perisinusoidal pattern, seen on trichrome stain. NAFLD is marked with macrovesicular steatosis, which is seen as empty lobules representing former fatty vesicles within hepatocytes from which fat was lost during tissue fixation and processing. Inflammation is demonstrated with neutrophilic, histiocytic, and lymphocytic infiltration into the liver parenchyma and hepatocellular ballooning degeneration. In alcoholic steatohepatitis, hepatocytes may have Mallory-Denk bodies, which are eosinophilic inclusion bodies within hepatocytes, and neutrophilic satellitosis.

2) Irreversible damage: liver cirrhosis (slide: cirrhosis).

A 56 year old homeless man comes to free clinic for checkup and a free meal. He has no complaints other than that his friends have been noticing that his eyes have been turning yellow for the past few months. PMH is significant for HTN, HL, chronic HCV infection, and anemia. FH is

significant for some cancer in his estranged father. He does not smoke but drinks "a lot," and uses heroin on a daily basis. His vitals were T 98.1°F, HR 90 bpm, 146/91 mmHg, RR 18, and 95% sat on RA. Physical exam revealed a cachexic male with scleral icterus, ascites with shifting dullness, and bilateral lower extremities edema up to shin. His labs were significant for Na 129, Cr 1.4, total bilirubin 4.2, AST 45, ALT 39. He was told to go to the emergency room. However, he never showed up and was found dead three days with needles and syringes beside him. An autopsy was performed and his liver biopsy is provided below.

Q1: If he did reach the ER and labs were drawn, what would you expect his LFT to be?
A1: Absolute number of AST and ALT and ratio of AST/ALT are telling of type and severity of liver damage. This patient had had chronic HCV infection along with daily alcohol use, and his physical exam showed evidence suggestive of cirrhosis. AST and ALT may be within normal range at end stage liver disease due to diminishing hepatic synthetic function.

Acute hepatic ischemia or toxic injury: hundreds or even thousands, AST:ALT ratio 1:1.
Acute viral hepatitis: typically in range of low to mid hundreds, AST:ALT ratio 1:1.
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Chronic hepatitis: around one hundred.
Cirrhosis: lower than one hundred, may be normal at end stage liver disease.

Q2: His abdominal exam was difficult due to ascites, and the student was not able to palpate any liver at all. What would he feel if he were more skilled or there wasn't any ascites?
A2: This patient likely has liver cirrhosis, and liver is typically *normal* in size, or may even be shrunken. However, the liver would be firm and non-tender to palpation. This is in contrast to fatty liver disease, acute hepatitis, or right heart failure, in which liver span would be enlarged and may be tender to palpation. If there were a nodule felt on the liver surface, then a primary hepatocellular carcinoma or liver metastasis is suspected.

Q3: Autopsy of the liver of the patient is expected to show what features?
A3: Hepatic cirrhosis shows marked bridging fibrosis on biopsy. Fibrosis comes in different forms. Chicken wire fibrosis refers to perisinusoidal collagen deposits between individual hepatocytes, and this is commonly seen in NASH and alcoholic liver disease and may provide a clue to the etiology of the cirrhosis. Bridging fibrosis describes thick collagen bands linking individual portal triads and central zones. Hepatocytes may also demonstrate ballooning degeneration and Mallory-Denk bodies.

3) Chronic granulomatous disease: tuberculosis (slide tuberculosis granulomatous inflammation)

A 50 year old Caucasian male comes to clinic for 3 months of chronic cough and increasing shortness of breath. The cough was productive with yellowish sputum, but recently he has seen streaks and clots of blood. There were nights in which his pillow was completely soaked with sweat. Review of systems revealed a weight loss of 20 lbs. over this period and some resting chest pain. There was no recent travel. PMH includes emphysema and HL. FH was noncontributory. He does not drink or use illegal drugs but has smoked one pack per day for the last 30 years, and was just released from prison 6 months ago. His vitals were T 97.9°F, HR 85 bpm, 132/82 mmHg, RR

21, and 97% sat on RA. Physical exam revealed bibasilar crackles but otherwise unremarkable. A representative biopsy is provided below.

Q1: What is the next step?
A1: This patient's symptoms are concerning for two things, pulmonary tuberculosis given hemoptysis, weight loss, and night sweats, and lung cancer given weight loss and chronic smoking. In an outpatient setting, anytime tuberculosis is suspected, the patient should be put into negative pressure isolation room and healthcare personnel should wear N95 masks around him. Appropriate workup then includes chest x-ray, interferon gamma release assay, or tuberculin skin test, and sputum acid fast or auramine staining and culture.

Q2: Sputum sample was acquired from the patient, what are you looking for?
A2: Sputum sample is used for two purposes: acid-fast or auramine staining to rapidly assess presence of *Mycobacterium tuberculosis*, and culture for drug sensitivity and specific species identification. Typically three sputum samples are collected, each 24 hours apart, and three negative cultures are required to rule out tuberculosis.

4) Chronic granulation tissue: keloid (slide for granulation tissue)
A 32 year old African-American woman comes to clinic for an enlarging "scab" on her left forearm. She states that she accidentally cut her arm with a knife while cooking dinner three months ago. She recalled the cut was "not deep" and was about 1 inch in length. A scab formed, but ever since the skin never really looked the same, and the scab seemed to enlarge over time. She has no significant PMH and FH, and is a teetotaler who has never smoked or used illegal drugs. Her vitals were within normal range. Physical exam revealed protruding dark scar tissue measuring 2 inches where she had cut herself. A protruding biopsy is shown below.

Q1: What is the diagnosis? And what about hypertrophic scar?
A1: Given the appearance of the wound, a keloid is the most likely diagnosis. It is more common in blacks than in other ethnicities, can arise spontaneously or after an injury. A hypertrophic scar can appear similar to a keloid, but the scar hypertrophy does not extend beyond the area of injury in contrast to a keloid, which often extends beyond the margin of the wound.

Q2: What is the cellular and molecular mechanism underlying keloid?
A2: Excessive formation of the components of the repair process, including hyperproliferation and activation of fibroblasts causing excessive laying down of collagen type III. PDGF, VEGF, and TGFβ signaling pathways are all implicated in the process.

5) Cervical cancer
A 41 year old G4P0 woman presents with irregular vaginal bleeding and postcoital bleeding. She is pre-menopausal and her period was normally regular with 28 day cycles. Vaginal bleeding was described as mucoid with slight odor. There is no dysuria, constipation, or any other constitutive symptoms. Her past medical history is non-contributory, and she has never had any Pap smears before. She worked in the entertainment industry and has had multiple sexual contacts with inconsistent condom use since first sexual activity at age 14. Her vitals were 37.2, 80, 124/89, 20, 99%, with normal general physical exam. Pelvic exam revealed erythema surrounding the cervical os. A Pap smear was taken, followed by colposcopy and biopsy

Q1: Where does cervical cancer typically arise?
A1: The cervix is composed of endocervix, transformation zone, and exocervix. Endocervix is rich in glands while the exocervix is composed of stratified squamous epithelial cells. The area between these cell types is called the transformation zone or squamocolumnar junction. Most cervical cancers arise from the transformation zone.

Q2: What are ways to acquire samples for cervical cancer screening and diagnosis?
A2: Exfoliative cytology and biopsy. Cytology, or Pap smear, is good for screening but it only gives information about cell morphology and no structure or histology. Normal cervical squamous cells are polygonal with bluish or pink hue, and small regular nuclei. Increasing nuclear to cytoplasmic ratio, nuclear irregularity and hyperchromasia warrant further workup. Biopsy is typically performed after an abnormal pap smear or if the patient has symptoms worrisome for cervical cancer. Biopsy is obtained with assistance of colposcopy, in which the cervix is visualized under magnification, and a biopsy is performed of suspicious lesion.

Q3: What is are current guideline for screening for cervical cancer?
A3: Current guidelines from US Preventive Services and Taskforce:
Age below 21: do not screen
Age 21-29: cytology every 3 years
Age 30-65: cytology alone every 3 years, or cytology with HPV testing every 5 years
Age above 65 or with normal screening before: do not screen. Women with history of cervical precancerous lesions should continue to be screened.
Women with hysterectomy *and* removal of cervix and no history of cervical cancer or precancerous lesions: do not screen

6) Prostate cancer
A 76 year old African-American man presents for the first time to clinic to establish care. He has no current complaints besides blurry vision and frequent urination at night with weak stream that has been going on for at least 5 years. His vitals were 37.0, 72, 152/87, 16, 95%. General physical exam cataracts, bibasilar respiratory crackles, and 1+ bilateral lower extremity edema. Digital rectal exam revealed asymmetrically enlarged prostate with nodules. Labs showed PSA of 4. A transrectal biopsy was taken under ultrasound guidance.

Q1: How does prostate cancer present differently than BPH?
A1: The prostate is divided into peripheral zone, transitional zone, and periurethral zone. BPH more commonly arises from periurethral zone, and therefore causes more urinary symptoms. On the other hand, prostate cancer occurs more in peripheral zone, especially in the posterior region near the rectum. Therefore most prostate cancer patients have no urinary symptoms, and if they do, the symptoms are attributed to concurrent BPH. As a result, 80% of patients who have had a prostate biopsy have done so because of abnormal PSA, with the rest because of an abnormal rectal exam.

Q2: How does prostate cancer appear on histology and what is a Gleason score?
A2: Prostate carcinomas are typically adenocarcinomas, or cancers forming glandular structures. A very well-differentiated tumor with many well-differentiated glands is graded as 1, and a poorly-

differentiated tumor with anaplastic tumor cells in sheets and cords (essentially no glands) is graded as 5. Gleason score is the sum of two most prevalent grades, with the dominant grade listed first and the secondary grade listed second. For example, a biopsy with mostly grade 3 tumor glands, and a few patchy areas of grade 4 tumor glands, would be scored as 3+4 = 7. The combined score is then used for prognostic purposes.

7) Breast cancer

A 52 year old Caucasian G1P1 post-menopausal woman presents with redness, pain, and "dimples" on her left breast. She stated that she first noticed discoloration of her left breast 2 months ago that has been increasing in size. She also has associated pain and tenderness with her breast without discharge from the nipple. She has had one normal mammogram 6 years before, but has not had any more mammograms since because she lost her health insurance. Her family history is significant for two aunts with breast cancer in their 70s. Her vitals were stable and physical exam revealed skin erythema on upper left and lower quadrants of her left breast with peau d'orange appearance, and 2 cm left axillary lymph nodes. Mammogram showed a calcified tumor mass in left upper quadrant. A biopsy was performed.

Q1: A core biopsy was taken revealing invasive ductal carcinoma. How is it graded?
A1: The modified Bloom-Richardson grading scheme assesses tubule/gland formation, nuclear pleomorphism, and mitotic counts, with individual scores added together to yield a tumor grade.

Q2: What is the reason behind her dimpled skin surface (peau d'orange change), and what would histology show?
A2: Her dire physical exam findings are suggestive of inflammatory breast carcinoma, due to obstruction of dermal lymphatic vessels by the tumor. Most inflammatory breast cancers are due invasive ductal carcinomas.

Q3: What are the some common immunohistochemistry to be ordered for this patient?
A3: Typically estrogen receptor, progesterone receptor, and HER-2 protein are stained because there exist targeted therapies against these, such as tamoxifen and trastuzumab.

8) Colon cancer

A 75 year old Caucasian man presents to clinic with fatigue. He states that he has been more tired than usual for the past 5 months, with shortness of breath when walking around the park, an exercise he used to do without any difficulties with his wife. Labs revealed Hb 8.9, Hct 43%, MCV 91.

Q1: What is the next step?
A1: In the geriatric population there are three etiologies for anemia of about equal distribution: iron or B9/B12 deficiencies, chronic disease such as chronic kidney diseases and others, and unknown causes. Chronic blood loss including gastrointestinal bleeding is an important cause of iron-deficiency anemia, and colon cancer is of primary concern in this age group. As a result, iron panel, stool examination for occult blood, and a colonoscopy are appropriate next steps.

Q2: What are screening guidelines for colon cancer, and why?
A2: Routine screening for patient with average colon cancer risk from US Preventive Services:

Age 50-75: colonoscopy every 10 years, sigmoidoscopy + fecal occult blood test (FOBT) every 5 years, or annual FOBT.
Age 76-85: no routine screening
Age above 85: do not screen.

Screening guidelines in patient without hereditary syndromes or symptoms are made as balance between maximum benefit and least harm for most patients, with economics consideration. Current guidelines states that screening should begin at age 50 for two reasons: First, most colon cancer is derived from polyps transforming into adenocarcinomas, and second, the prevalence of adenomatous polyps increases after age 50 to the point where they affect approximately 50% of the population in Western countries.

Q3: How does colon cancer arise from polyps?
A3: During colonoscopy several types of polyps may be found; these include adenomatous, hyperplastic, inflammatory pseudopolyps, submucosal, and hamartomatous polyps. Of these, adenomatous and hyperplastic are the most common source of malignant transformation. Of these two, adenomatous polyps is the most common cause of colon cancer, and is morphologically described as sessile, pedunculated, flat, or depressed, and pathologically described as tubular, tubulovillous, and villous. Adenomatous polyps with larger size (> 1cm), higher proportion of villous histology, and higher number have higher malignant potential. Left-sided hyperplastic polyps show sawtooth crypts on histology, and are composed of cells that lack dysplasia. Right-sided sessile serrated adenomas show crypt irregularity, and have a high rate of DNA methylation and BRAF mutations. The natural history and risk of progression of sessile serrated polyps is under intense investigation, as some may have higher malignant transformation potential than adenomatous polyps.

Q4: What are molecular steps involved in adenomatous polyp transformation to adenocarcinoma?
A4: Sequential loss of function mutation in APC, gain of function mutation in K-ras, and finally loss of function in p53.

Block 2: Gastrointestinal System II

1) Reversible damage: non-alcoholic fatty liver disease (slide: steatosis)

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Q2: The patient also has mildly elevated liver enzymes with AST and ALT in 150s range. His viral panels are normal. What does he have, and what is worrisome in this condition?
A2: Elevation of liver enzymes in a patient with metabolic syndrome who does not drink alcohol and otherwise has no history of hepatitis is likely due to non-alcoholic fatty liver disease, or NAFLD. NAFLD is generally a reversible condition, but if left untreated can progress to non-alcoholic steatohepatitis, or NASH.

Q3: NAFLD was likely in this patient, but NASH or cirrhosis are not definitively ruled out. Therefore he underwent a liver biopsy to assess his condition. How are NAFLD and NASH different and what are expected to be shown by biopsy?
A3: NAFLD is a spectrum of non-alcoholic diseases subdivided into NAFL and NASH. In NAFL, there is no evidence of inflammation, although steatosis is present. NAFL may progress to NASH, which has inflammation and may appear indistinguishable from alcoholic steatohepatitis. NASH can progress to fibrosis or cirrhosis if left untreated. Fibrosis has a distinctive "chicken wire" perisinusoidal pattern, seen on trichrome stain. NAFLD is marked with macrovesicular steatosis, which is seen as empty lobules representing former fatty vesicles within hepatocytes from which fat was lost during tissue fixation and processing. Inflammation is demonstrated with neutrophilic, histiocytic, and lymphocytic infiltration into the liver parenchyma and hepatocellular ballooning degeneration. In alcoholic steatohepatitis, hepatocytes may have Mallory-Denk bodies, which are eosinophilic inclusion bodies within hepatocytes, and neutrophilic satellitosis.

2) Irreversible damage: liver cirrhosis (slide: cirrhosis)

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heroin on a daily basis. His vitals were T 98.1°F, HR 90 bpm, 146/91 mmHg, RR 18, and 95% sat on RA. Physical exam revealed a cachexic male with scleral icterus, ascites with shifting dullness, and bilateral lower extremities edema up to shin. His labs were significant for Na 129, Cr 1.4, total bilirubin 4.2, AST 45, ALT 39. He was told to go to the emergency room. However, he never showed up and was found dead three days with needles and syringes beside him. An autopsy was performed and his liver biopsy is provided below.

Q1: If he did reach the ER and labs were drawn, what would you expect his LFT to be?
A1: Absolute number of AST and ALT and ratio of AST/ALT are telling of type and severity of liver damage. This patient had had chronic HCV infection along with daily alcohol use, and his physical exam showed evidence suggestive of cirrhosis. AST and ALT may be within normal range at end stage liver disease due to diminishing hepatic synthetic function.

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Q2: His abdominal exam was difficult due to ascites, and the student was not able to palpate any liver at all. What would he feel if he were more skilled or there wasn't any ascites?
A2: This patient likely has liver cirrhosis, and liver is typically *normal* in size, or may even be shrunken. However, the liver would be firm and non-tender to palpation. This is in contrast to fatty liver disease, acute hepatitis, or right heart failure, in which liver span would be enlarged and may be tender to palpation. If there were a nodule felt on the liver surface, then a primary hepatocellular carcinoma or liver metastasis is suspected.

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A3: Hepatic cirrhosis shows marked bridging fibrosis on biopsy. Fibrosis comes in different forms. Chicken wire fibrosis refers to perisinusoidal collagen deposits between individual hepatocytes, and this is commonly seen in NASH and alcoholic liver disease and may provide a clue to the etiology of the cirrhosis. Bridging fibrosis describes thick collagen bands linking individual portal triads and central zones. Hepatocytes may also demonstrate ballooning degeneration and Mallory-Denk bodies.

3) Other liver damages: viral hepatitis and acetaminophen toxicity

A 30 year old male presents with jaundice. He just returned from a trip in India last week. His labs show AST and ALT in 300s range. A viral panel revealed positive hepatitis A infection.

Q1: What would a biopsy of his liver show?
A1: In acute viral hepatitis, the liver parenchyma is infiltrated with predominantly lymphocytes, and hepatocytes may undergo necrosis, ranging from individual necrotic hepatocytes to confluent necrosis showing pink bridging necrosis linking from one liver lobule to another on biopsy.

A 29 year old female was admitted to the ER after she was found to have ingested "a bottle" of Tylenol six hours ago. Her plasma acetaminophen value was found to be above toxic levels, and N-acetylcysteine was given to her.

Q2: What would liver biopsy show?
A2: Coagulative necrosis is a distinguishing feature of acetaminophen toxicity. Biopsy would show loss of hepatocellular nuclei and eosinophilic appearing cytoplasm, especially in zone 3 (submassive necrosis), but necrosis may progress to involve the entire hepatic lobule (massive necrosis).

4) Colon cancer

A 75 year old Caucasian man presents to clinic with fatigue. He states that he has been more tired than usual for the past 5 months, with shortness of breath when walking around the park, an exercise he used to do without any difficulties with his wife. Labs revealed Hb 8.9, Hct 43%, MCV 91.

Q1: What is the next step?
A1: In the geriatric population there are three etiologies for anemia of about equal distribution: iron or B9/B12 deficiencies, chronic disease such as chronic kidney diseases and others, and unknown causes. Chronic blood loss including gastrointestinal bleeding is an important cause of iron-deficiency anemia, and colon cancer is of primary concern in this age group. As a result, iron panel, stool examination for occult blood, and a colonoscopy are appropriate next steps.

Q2: What are screening guidelines for colon cancer, and why?
A2: Routine screening for patient with average colon cancer risk from US Preventive Services:
Age 50-75: colonoscopy every 10 years, sigmoidoscopy + fecal occult blood test (FOBT) every 5 years, or annual FOBT.
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Screening guidelines in patient without hereditary syndromes or symptoms are made as balance between maximum benefit and least harm for most patients, with economics consideration. Current guidelines states that screening should begin at age 50 for two reasons: First, most colon cancer is derived from polyps transforming into adenocarcinomas, and second, the prevalence of adenomatous polyps increases after age 50 to the point where they affect approximately 50% of the population in Western countries.

Q3: How does colon cancer arise from polyps?
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sided sessile serrated adenomas show crypt irregularity, and have a high rate of DNA methylation and BRAF mutations. The natural history and risk of progression of sessile serrated polyps is under intense investigation, as some may have higher malignant transformation potential than adenomatous polyps.

Q4: What are molecular steps involved in adenomatous polyp transformation to adenocarcinoma?
A4: Sequential loss of function mutation in APC, gain of function mutation in K-ras, and finally loss of function in p53.

5) Inflammatory bowel disease

A 17 year old male comes with unusual fatigue. History is significant for abdominal pain, chronic diarrhea sometimes with blood, and sometimes pain with defecation. There has been a 15-lb weight loss in the last six months. No contributory PMH or FH, and exam is normal for a teenager except skin pallor.

Q1: What is the most likely diagnosis?
A1: Inflammatory bowel disease (IBD) due to chronicity of disease, bloody diarrhea causing anemia or pallor, and weight loss. However, it is also important to obtain microbiology labs to rule out infection in addition to workup for IBD.

Q2: How is IBD diagnosed?
A2: Besides CBC which may show anemia and FOBT showing blood in stool, fecal leukocytes and fecal calprotectin are useful laboratory tests to demonstrate inflammation. Fecal calprotectin is more specific for non-infectious inflammation of the bowel. Ultimately IBD is diagnosed with endoscopy with biopsy.

Q3: What would endoscopy show?
A3: IBD is categorized into Crohn's disease and ulcerative colitis, although in a subset of patients it may be impossible to differentiate between the two. Classically Crohn's disease shows patchy transmural mucosal inflammation that can lead to abscess or fistula formation, can involve the entirety of the GI tract, and usually has cobblestone or skip lesions. Ulcerative colitis shows mucosal-restricted inflammation that has no fistula formation potential, is usually limited to colon (although distal ileum can be involved in "backwash ileitis"), often left sided, and lesions are normally continuous (i.e. no skip areas in untreated ulcerative colitis).

Q4: What are some key distinguishing features of IBD in pathology?
A4: Crohn's disease may present with noncaseating granulomas, deep knife-like fissures, and patchy transmural inflammation; while ulcerative colitis involves the rectum, shows diffuse continuous disease, and is generally mucosal restricted.

Q5: This patient was diagnosed with ulcerative colitis and put on 5-ASA for maintenance and steroids for acute flares. What is the next step?
A5: Patients with IBD have increased risk of colon cancer; therefore, current guidelines recommend beginning colonoscopy eight years after formal IBD diagnosis, and annual colonoscopy afterwards.

6) Peptic ulcer disease

A 56 year old male comes to the office for 3 weeks of abdominal pain, described as sharp and located in the midgastrum, sometimes associated with eating. He also noticed that for the past 2 weeks he has had episodic black tarry stool. He had suffered a fall at work approximately one two months ago and was taking daily ibuprofen to relieve his pain. No contributory PMH and FH. An upper endoscopy with biopsy was performed.

Q1: What is the most likely diagnosis?

A1: He likely has peptic ulcer disease due to NSAID use, which prevents synthesis of mucosal-protective prostaglandins. Other causes of peptic ulcer disease include *H. pylori* infection and chronic corticosteroid use. Peptic ulcers can be located in the stomach or duodenum. Classically gastric ulcers worsen with food and duodenal ulcers are relieved with food. In addition, duodenal ulcers are associated with *H. pylori* infection if not related to NSAID use.

Q2: What would endoscopy and biopsy show?

A2: Endoscopy would show friable mucosa with central ulceration and possible active bleeding. Biopsy of lesion is used to confirm diagnosis and rule out more serious conditions such as gastric cancer. Peptic ulcer biopsy would show inflammation extending from mucosa potentially to submucosa, and erosion into arterioles can cause hemorrhage. Because *H. pylori* is a common cause of peptic ulcers, gastric ulcer biopsies routinely undergo examination for *H. pylori*. Biopsy may reveal cork-screwed or seagull wing-shaped bacteria.

7) Chronic autoimmune gastritis: pernicious anemia

A 75 year old female comes to the clinic with imbalance because she cannot really feel her footing. Physical exam suggested imbalance from peripheral neuropathy and CBC revealed megaloblastic anemia.

Q1: What is the likely diagnosis?

A1: She is likely to have B12 deficiency from pernicious anemia. B12 absorption requires intrinsic factor which is produced from parietal cells of the stomach. In autoimmune gastritis, parietal cells are destroyed, leading to B12 deficiency, which causes dysfunction of dorsal columns leading to imbalance and megaloblastic anemia.

8) Gastroesophageal reflux disease/Barrett's esophagitis/adenocarcinoma

A 55 year old obese male comes to the clinic with burning sensation in his chest especially after meals, and he also sometimes wakes up with a sour taste in his mouth. Upper endoscopy with biopsy was performed, revealing esophagitis at the GE junction, and a diagnosis of GERD was made.

Q1: What would the endoscopy reveal?

A1: Upper endoscopy is used to assess degree of esophagitis and rule out other more serious conditions such as esophageal cancer. In GERD upper endoscopy would show inflammation and ulcers at the GE junction graded depending on number and size or extent of mucosal breaks in relation to esophageal circumference.

Q2: Where is biopsy typically taken and what would it show?

A2: Biopsy is taken at Z-line (columnar-squamous junction) and few centimeters above and below. Biopsy would reveal chronic-active inflammation and increased depth of basal layer of squamous mucosa due to basal layer hyperplasia to increase regenerative capacity to replace the damaged superficial epithelium (from stomach acid). In addition, papillary elongation and spongiosis (edema of intercellular spaces) can be seen.

The patient's endoscopy showed severe erosive esophagitis, and he was put on a proton pump inhibitor along with dietary modification and weight reduction plan. However, since loss of his job and health insurance he has been fairly non-compliant with any of these. His symptoms worsened, and he finally got insurance when Affordable Care Act started. A repeat endoscopy was performed to assess his disease progression.

Q3: He has not been on treatment for years since the initial diagnosis. What might the biopsy show? What is this patient at risk for developing?
A3: Without proper treatment or response this patient's chronic GERD is likely to have progressed resulting in severe esophagitis, which may lead to Barrett's esophagitis, which is a metaplastic condition requiring histological diagnosis. In Barrett's esophagitis, the normally squamous esophageal epithelium undergoes columnar metaplasia with goblet cell metaplasia, so-called "intestinal epithelium." Having Barrett's esophagitis itself is a risk factor for developing esophageal adenocarcinoma, especially in the distal one third of the esophagus. Therefore AGA guidelines recommend endoscopic screening for patients with Barrett's esophagitis if he has multiple risk factors, including male gender, age over 50, white race, chronic GERD, hiatal hernia, and obesity.

9) Celiac disease

A 24 year old woman comes to the clinic with 7 months of fatigue and unintentional weight loss. Careful review of systems revealed chronic diarrhea with oily stools. She has no travel history within the last two years. Physical exam was largely normal with exception of few papules on her elbows that she said at times were extremely pruritic.

Q1: What is the most likely diagnosis?
A1: Chronicity of disease, weight loss, and steatorrhea suggest some malabsorption problem. Her lack of recent travels and elbow lesions (dermatitis herpetiformis), are suggestive of celiac disease.

Q2: What is the next step to establish the diagnosis?
A2: Laboratory and endoscopy with biopsy are necessary for diagnosis. Anti-tissue transglutaminase (IgA) and total IgA are usually the first step in diagnosis. Patients with low IgA from selective IgA deficiency should have IgG anti-deamidated gliadin or anti-endomysial antibodies tested. Patients with positive laboratory findings or with high probability of celiac disease should undergo small bowel endoscopy with biopsy.

Q3: What are key features of celiac disease on histology?
A3: Classically blunting of villi in duodenal epithelium can be directly visualized via endoscopy. Biopsy would reveal increased intraepithelial lymphocytes, mucosal atrophy with villi blunting or flattening, and crypt hyperplasia.

10) Pancreatic disease

A 50 year old patient with stage II pancreatic adenocarcinoma that was discovered when he had painless jaundice one months ago presented to the ED with sharp epigastric pain that occurred suddenly a few hours earlier. Two days ago he had an ERCP done to assess biliary obstruction.

Q1: What is the most likely diagnosis to explain his current symptoms?
A1: Post-ERCP pancreatitis.

Q2: What would pancreas biopsy show?
A2: Neutrophilic infiltrate with necrosis of pancreatic acinar cells, and adjacent fat necrosis due to enzyme release from necrosis of acinar cells. Hemorrhagic foci may be seen.

Q3: This gentleman also had adenocarcinoma of the pancreas; what would his biopsy show?
A3: The pancreas is composed of endocrine islets (alpha and beta cells), exocrine cells, and ductal epithelium. The most common type of pancreatic cancer arises from neoplastic transformation of ductal cells (ductal adenocarcinoma), followed distantly by carcinoma of acinar cells. Adenocarcinomas are tumors showing glandular differentiation, and ranging from well differentiated with many glandular structures to poorly differentiated with poor gland formation and dense stromal fibrosis.

11) Acute appendicitis

A 28 year old athlete comes to the ED with intractable abdominal pain. The pain is located in his right lower quadrant, sharp, and developed within an hour this morning. His vitals showed low grade fever, and physical exam was remarkable for positive rebound abdominal tenderness.

Q1: What is the most likely diagnosis, and what are treatment options?
A1: He is likely to have acute appendicitis. The most feared complication is perforation of the appendix leading to peritonitis and sepsis. Following stabilization with fluid, surgical removal of the inflamed appendix is standard treatment.

Q2: What would the biopsy from his resected appendix show?
A2: Appendiceal mucosal inflammation and necrosis, with infiltration of neutrophils into or through the muscularis propria (wall of appendix).

12) Hemochromatosis

A 50 year old man comes to the office at his wife's urging, who is concerned that he looks "perennially tanned" for the past few months although it's winter time and he never used a tanning bed. Review of charts is remarkable for mildly elevated liver enzymes for the past few years although patient states he is a teetotaler and never had hepatitis. Review of systems is significant for increased thirst and urination at night, especially in the last few months.

Q1: What is the likely diagnosis?
A1: Patient's skin pigmentation, newly developed symptoms of diabetes, and elevated liver enzymes suggest iron overload pathology, likely hemochromatosis.

Q2: What is the next step in diagnosis? Is biopsy necessary?

A2: The first step would be to repeat liver function tests and conduct an iron study, which typically includes serum iron concentration, ferritin, and transferrin saturation. Genetic testing is now good enough to diagnose hereditary hemochromatosis, and MRI is sensitive enough to assess iron overload within the liver, given proper operator techniques. However, liver biopsy is still required to assess severity of liver disease, obtain tissue for quantitative iron studies, and monitor for cirrhosis.

Q3: The patient's genetic testing confirmed a diagnosis of hemochromatosis, and because his liver enzymes have been elevated for years, he underwent liver biopsy. What is expected on biopsy?
A3: Liver biopsy assesses degree of iron overload via Prussian blue stain and extent of liver damage and fibrosis via H&E and trichrome stains on histology. Brown pigmentation of hepatocytes indicates iron deposition, and on Prussian blue this pigmentation usually starts at periportal periphery of the liver lobule (zone I) and with more advanced disease extends to the center (zone 3).

13) Amoebic colitis

A 30 year old woman comes to the office for three weeks of diarrhea. She returned from a backpacking trip in the countryside of Mexico a month ago, and one week after returning she started having watery diarrhea at first, followed by bloody stools with some mucus. Her vitals were stable and physical exam was remarkable for some diffuse abdominal pain upon palpation. Stool study revealed trophozoites.

Q1: What is the diagnosis? What is the most feared complication?
A1: Presence of trophozoites or cysts are suggestive of entamoeba infection, or intestinal *Entamoeba histolytica* amebiasis. Although most patients present with mild to severe dysentery symptoms, it can evolve to toxic megacolon or perforation if untreated, and may progress to amoebic abscesses in the liver.

Q2: The patient was sent home with metronidazole. If she were to have a biopsy, what would it show?
A2: Flask shaped ulcers with broad base in lamina propria, and trophozoites of *E. histolytica* may be seen. These trophozoites are round with a large cytoplasm containing a prominent nucleus and multiple vacuoles. They may also contain ingested red blood cells.

14) Cholecystitis

A 38 year old obese female comes to the ED for abdominal pain. The pain was sharp and 10 out of 10, located in her right upper quadrant and came on suddenly. She appeared very ill, and she was febrile with tachycardia. Physical exam was noted abdominal tenderness to palpation and positive Murphy's sign.

Q1: What are the diagnosis? How is it diagnosed and treated?
A1: Based on her symptoms she is likely to have acute cholecystitis. Her labs would reveal leukocytosis as well. Ultrasound is usually the first step in diagnosis, which could reveal thickened gallbladder wall indicating inflammation. If ultrasound is inconclusive, a HIDA scan is used to demonstrate biliary ductal system patency. For healthy patients, surgical removal of gallbladder is

preferred treatment, especially if done early. For older patients and those who are not surgical candidates, drainage may be required.

Q2: What would the sections of the removed gallbladder show?
A2: Thickened gallbladder wall from edema and hemorrhage in the muscular layer, with neutrophilic infiltration and necrosis. There may be calculi in the gallbladder lumen.

Block 3: Endocrine, Reproduction, and Metabolism II

1) Leiomyoma and leiomyosarcoma of uterus

A 65 year old G3P3 woman presents to clinic with spotty vaginal bleeding accompanied by vague lower abdominal pain for the last three months. She also noticed that sometimes she had to strain to pass stool or urine, but wasn't sure about the timing. She had menarche and menopause at age 12 and 55, respectively. Family and past medical histories are non-contributory. Her vitals were stable and pelvic exam revealed normal atrophied vagina and cervix with some scant blood, and a mass located at posterior body of the uterus.

Q1: What are the next steps?
A1: Any women presenting with vaginal bleeding after menopause need to be thoroughly worked up to rule out endometrial cancer. In this case, an endometrial biopsy is appropriate given her age and symptoms. Because a mass was palpated during examination, imaging is necessary to define the mass. Ultrasound, MRI, and CT are all useful modalities. It is important to note that imaging cannot readily differentiate between different types of mass, let alone a benign and malignant one.

Q2: An endometrial biopsy was obtained, which showed atrophic endometrial mucosa appropriate for the patient's postmenopausal status without evidence of malignancy. Her PET scan did not show abnormal foci of increased metabolic activity. Because of her age, a total hysterectomy was recommended. What are differential diagnoses for her uterine mass, and how does one differentiate among them?
A2: Differential diagnoses for uterine mass include leiomyoma, leiomyosarcoma, uterine adenomyoma, and metastatic disease. Clinical examination or imaging may differentiate among them; for example, uterus may be diffusely enlarged in adenomyosis, while a discrete mass may be palpated in a leiomyoma. However, pathology is required for definitive diagnosis, such as in distinguishing leiomyoma from leiomyosarcoma.

Q3: Her resected uterus showed numerous multiple white firm nodules on the anterior inferior surface of the organ. How does a leiomyoma appear histologically?
A3: Leiomyoma, also known as a fibroid, results from smooth muscle proliferation. It can develop within myometrium (intramural), underneath endometrium (submucosal), underneath uterine serosa (subserosal), and may protrude into uterine cavity (pedunculated). On histology they appear as nodules of spindle-shaped elongated smooth muscle cells appearing almost indistinguishable from surrounding normal myometrium.

Q4: Her resected uterus showed a single necrotic and hemorrhagic nodule on the anterior inferior surface of the organ. How does leiomyosarcoma differ from leiomyoma?
A4: Grossly leiomyosarcomas appear more "malignant." While a leiomyoma may have smooth well-defined borders, a leiomyosarcoma is often necrotic and/or hemorrhagic because uncontrolled mass outgrew its blood supply. Also, while leiomyomas may be multiple nodules, leiomyosarcoma tends to be solitary. On histology, rather than the bland spindle-shaped smooth muscle cells and organized and well-circumscribed appearance of leiomyoma, leiomyosarcoma cells are hypercellular, pleomorphic with different nuclear and cellular shapes, and have increased mitotic counts. Local invasion and tumor necrosis are often seen.

2) Teratomas (dermoid cyst and solid)

A 20 year old woman comes to the ER for acute abdominal pain. She said that pain, now 8/10, appeared suddenly in her lower right abdominal quadrant. A bedside ultrasound showed a complicated cystic mass in her right ovary. Because she was becoming hypotensive, an emergency laparoscopic cystectomy was performed.

Q1: What is a teratoma and how does it appear histologically?
A1: Teratoma is the most common type of germ cell tumor and is usually cystic, and more rarely solid. Mature cystic teratoma, also known as a dermoid cyst, is the most common teratoma type. It is benign although it has a very small chance of malignant transformation. Most patients with dermoid teratomas are asymptomatic, although in some cases the cystic mass can rupture causing peritoneal symptoms. Mature teratomas may contain well differentiated tissues derived from the ectoderm (hair and skin), mesoderm (muscle), and endoderm (gastrointestinal and respiratory).

Q2: What is immature teratoma?
A2: Immature teratoma is a rare type of teratoma, and is defined by presence of immature embryonal-type (generally immature neuroectodermal) tissue. Immature teratomas tend to occur in the first two decades of life.

3) Ovarian cystadenomas

A 67 year old woman presents to the ER for severe vomiting. She said vomiting and nausea started last night and are worsening. She has not been able to keep down any food, and there is also diffuse 7/10 pain in her abdomen. Review of systems is significant for weight loss of 20 lbs. in the last three months, and mild abdominal bloating and pain for a while now. Her vitals are stable, and physical exam is significant for a left adnexal mass.

Q1: What is the next step?
A1: Her symptoms of severe vomiting and inability to keep down food are worrisome for gastrointestinal obstruction. A plain abdominal X-ray is the first step for evaluation. Ultrasound is usually the next step to evaluate an ovarian mass.

Q2: Her vitals are stable, and an ultrasound was performed to evaluate the mass. What is the differential diagnosis, and what is the most likely cause of her symptoms?
A2: Ovarian mass can be a result of ectopic pregnancy, infections such as abscesses or hydrosalpinx, ovarian cysts, pedunculated fibroid, and tumors. Given her age and postmenopausal status, recent unexplained weight loss, normal vitals without fever, and vague chronic abdominal pain, ovarian cancer is suspected. Compression by the ovarian tumor or malignant peritoneal seeding of the cancer may explain her nausea and vomiting.

Q3: The patient was deemed fit for surgery and underwent open laparotomy to remove her ovaries and run through the bowels to check for peritoneal metastasis. What is the most common type of ovarian malignancy, and how does it differ from benign cystadenomas?
A3: The most common type of ovarian cancer is serous cystadenocarcinoma, and the high grade variant accounts for 70-80% of all malignant ovarian cancers. Grossly they can be both cystic and/or solid, and have papillary protrusions representing malignant growths in the inner surfaces of the cyst. This is in contrast to cystadenomas, whose inner surfaces are smooth with few if any papillations. Histologically cystadenocarcinoma form papillary projections into the lumen of the

cyst, as seen grossly, and the cells have high mitotic index and hyperchromatic nuclei. In addition, these tumors may form psammomma bodies, which appear as dark purple acellular rounded spheres derived from dystrophic calcification.

4) Cervical cancer

A 41 year old G4P0 woman presents with irregular vaginal bleeding and postcoital bleeding. She is pre-menopausal and her period was normally regular with 28 day cycles. Vaginal bleeding was described as mucoid with slight odor. There is no dysuria, constipation, or any other constitutive symptoms. Her past medical history is non-contributory, and she has never had any Pap smears before. She worked in the entertainment industry and has had multiple sexual contacts with inconsistent condom use since first sexual activity at age 14. Her vitals were 37.2, 80, 124/89, 20, 99%, with normal general physical exam. Pelvic exam revealed erythema surrounding the cervical os. A Pap smear was taken, followed by colposcopy and biopsy

Q1: Where does cervical cancer typically arise?
A1: The cervix is composed of endocervix, transformation zone, and exocervix. Endocervix is rich in glands while the exocervix is composed of stratified squamous epithelial cells. The area between these cell types is called the transformation zone or squamocolumnar junction. Most cervical cancers arise from the transformation zone.

Q2: What are ways to acquire samples for cervical cancer screening and diagnosis?
A2: Exfoliative cytology and biopsy. Cytology, or Pap smear, is good for screening but it only gives information about cell morphology and no structure or histology. Normal cervical squamous cells are polygonal with bluish or pink hue, and small regular nuclei. Increasing nuclear:cytoplasmic ratio, nuclear irregularity and hyperchromasia warrant further workup. Biopsy is typically performed after an abnormal pap smear or if the patient has symptoms worrisome for cervical cancer. Biopsy is obtained with assistance of colposcopy, in which the cervix is visualized under magnification, and a biopsy is performed of suspicious lesion.

Q3: What is are current guideline for screening for cervical cancer?
A3: Current guidelines from US Preventive Services and Taskforce:
Age below 21: do not screen
Age 21-29: cytology every 3 years
Age 30-65: cytology alone every 3 years, or cytology with HPV testing every 5 years
Age above 65 or with normal screening before: do not screen, Women with history of cervical precancerous lesions should continue to be screened.
Women with hysterectomy *and* removal of cervix and no history of cervical cancer or precancerous lesions: do not screen

5) Prostate cancer

A 76 year old African-American man presents for the first time to clinic to establish care. He has no current complaints besides blurry vision and frequent urination at night with weak stream that has been going on for at least 5 years. His vitals were 37.0, 72, 152/87, 16, 95%. General physical exam cataracts, bibasilar respiratory crackles, and 1+ bilateral lower extremity edema. Digital rectal exam revealed asymmetrically enlarged prostate with nodules. Labs showed PSA of 4. A transrectal biopsy was taken under ultrasound guidance.

Q1: How does prostate cancer present differently than BPH?
A1: The prostate is divided into peripheral zone, transitional zone, and periurethral zone. BPH more commonly arises from periurethral zone, and therefore causes more urinary symptoms. On the other hand, prostate cancer occurs more in peripheral zone, especially in the posterior region near the rectum. Therefore most prostate cancer patients have no urinary symptoms, and if they do, the symptoms are attributed to concurrent BPH. As a result, 80% of patients who have had a prostate biopsy have done so because of abnormal PSA, with the rest because of an abnormal rectal exam.

Q2: How does prostate cancer appear on histology and what is a Gleason score?
A2: Prostate carcinomas are typically adenocarcinomas, or cancers forming glandular structures. A very well-differentiated tumor with many well-differentiated glands is graded as 1, and a poorly-differentiated tumor with anaplastic tumor cells in sheets and cords (essentially no glands) is graded as 5. Gleason score is the sum of two most prevalent grades, with the dominant grade listed first and the secondary grade listed second. For example, a biopsy with mostly grade 3 tumor glands, and a few patchy areas of grade 4 tumor glands, would be scored as 3+4 = 7. The combined score is then used for prognostic purposes.

6) Fibroadenoma of the breast
A 30 year old woman comes to the physician for a lump she felt in her right breast. She first noticed this lump six months ago, and it seemed to be more noticeable in synchronization with her regular menstrual cycles. She has never had a mammogram. Her vitals are normal and physical exam revealed no lymphadenopathy but a discrete mobile rubbery mass was palpated in outer upper quadrant of her right breast.

Q1: What is the next step?
A1: Although the patient is young and the exam was relatively reassuring, the mass should be investigated. Since she has never had any imaging such as mammogram, an ultrasound of the breast is appropriate.

Q2: Ultrasound revealed a solid 2.5 cm mass in her right breast, an ultrasound guided core biopsy was performed, confirming the diagnosis of fibroadenoma. What would histology show?
A2: Fibroadenoma is a benign biphasic fibroepithelial tumor. Depending on the exact pattern of proliferation, ductal compression can occur causing the ducts to appear as slits in a sea of stromal tissue.

7) Breast cancer
A 52 year old Caucasian G1P1 post-menopausal woman presents with redness, pain, and "dimples" on her left breast. She stated that she first noticed discoloration of her left breast 2 months ago that has been increasing in size. She also has associated pain and tenderness with her breast without discharge from the nipple. She has had one normal mammogram 6 years before, but has not had any more mammograms since because she lost her health insurance. Her family history is significant for two aunts with breast cancer in their 70s. Her vitals were stable and physical exam revealed skin erythema on upper left and lower quadrants of her left breast with peau d'orange

appearance, and 2 cm left axillary lymph nodes. Mammogram showed a calcified tumor mass in left upper quadrant. A biopsy was performed.

Q1: A core biopsy was taken revealing invasive ductal carcinoma. How is it graded?
A1: The modified Bloom-Richardson grading scheme assesses tubule/gland formation, nuclear pleomorphism, and mitotic counts, with individual scores added together to yield a tumor grade.

Q2: What is the reason behind her dimpled skin surface (peau d'orange change), and what would histology show?
A2: Her dire physical exam findings are suggestive of inflammatory breast carcinoma, due to obstruction of dermal lymphatic vessels by the tumor. Most inflammatory breast cancers are due invasive ductal carcinomas.

Q3: What are the some common immunohistochemistry to be ordered for this patient?
A3: Typically estrogen receptor, progesterone receptor, and HER-2 protein are stained because there exist targeted therapies against these, such as tamoxifen and trastuzumab.

Block 4: Cardiovascular System II

1) Acute rheumatic endocarditis

A 13 year old boy who recently emigrated from Somalia was brought in by his mother to free pediatric clinic for increasing tiredness and inability to keep up with his peers in his PE class. Through a translator the mother says that the boy had suffered what appeared to be an episode of untreated sore throat years ago while still in Somalia, and recently he has been experiencing knee pain thought due to playing too much soccer with neighbor kids. But otherwise he has been fairly normal like other children on his block. Physical exam revealed a boy 40% percentile for height and weight, and a grade IV/VI systolic murmur in apex region of heart, and swollen right knee joint.

Q1: What is the most likely cause?
A1: Acute rheumatic fever.

Q2: What is the pathophysiology underlying rheumatic carditis?
A2: It is important to note that clinical sequelae of rheumatic fever are due to host immune responses against a bacterial antigen, rather than the infection itself. It is thought that antibodies and CD4+ T cells directed against Group A streptococcal M proteins can in some cases recognize cardiac self antigens, and cause the host immune system to attack self tissues.

Q3: The boy was put on penicillin. Unfortunately, two months after the office visit he was hit and mortally wounded by a drunk driver who drove onto the soccer field. An autopsy was performed. What would the sections of his heart show?
A3: Carditis in rheumatic fever is not just limited to the valves, but can affect all layers of the heart (pancarditis). On autopsy the pericardium may be thickened because of fibrin deposit with inflammatory infiltrate ("bread and butter" pericarditis). The myocardium may likewise be invaded by inflammatory cells, plump macrophages called Anitschkow cells, or macrophages with linear condensed chromatin appearing as a caterpillar in the middle may be present, as are Aschoff bodies, which resemble granulomas with lymphocytic infiltrate and macrophages surrounded by fibrin deposits. The valves may show inflammatory foci with fibrinoid necrosis and vegetations, and, as a result of organization of acute inflammation, subsequent fibrosis in longstanding RF. The mitral valve is predominantly affected, but other valves, such as the aortic valve, may also be involved and may be the most clinically important in some cases.

2) Infectious endocarditis

A 24 year old homeless man was brought into the emergency room by his friend for fever with shaking chills and new onset shortness of breath. The man managed to tell the on-call physician that he had difficulty breathing accompanied with profuse sweating that has been getting increasingly worse. An EKG was performed to rule out acute coronary syndromes, but it only showed sinus tachycardia. Physical exam revealed fever, needle track marks on bilateral upper extremities, and a holosystolic murmur on right lower sternal border.

Q1: What is the most likely diagnosis explaining the patient's symptoms?
A1: Given fever, murmur, and needle track marks, the most likely diagnosis infective (bacterial) endocarditis of tricuspid valve, the most frequent site of endocarditis for IV drug users, complicated by heart failure from tricuspid regurgitation or possible septic emboli to the lungs. He

may have had endocarditis for days if not weeks, but only showed up to the emergency room due to shortness of breath. Most cases of endocarditis are left-sided, but IV drug users suffer from (right-sided) tricuspid endocarditis due to injecting into venous system. Particulates from bacterial vegetations of the tricuspid valve break off and lodge into pulmonary veins (septic pulmonary embolism) which may cause pulmonary infarcts or infection (pneumonia).

Q2: What is the most likely organism in this case?
A2: For an IV drug user presumably with native valves, a skin organism such as *S. aureus* is the most likely source of his infection, followed by *S .viridans* spp. On the other hand, *S. aureus* and *S. viridans* spp. contribute roughly equally on non-IV drug users.

Q3: While waiting on the gurney the patient left the hospital against medical advice because of heroin withdrawal. Two days later he was found dead lying on the street. An autopsy was performed. What would the sections of his valve show?
A3: Valvular inflammation with neutrophilic (acute) or lymphohistiocytic (chronic) infiltrates, fibrin, and bacteria. Fibrinous bacterial vegetations may also be observed macroscopically on the valves.

3) Myocardial infarction

A 76-year-old man was brought to the emergency room by his wife for chest pain that wouldn't go away. He said about three days ago he was mowing his lawn when he had sudden pressure-like sensation behind his sternum that radiated to his left arm, accompanied by profuse shortness of breath and diffuse sweating. EKG reveals abnormalities. Cardiac troponin was drawn. He was started on medication.

Q1: What is the natural progression of ischemic stress on myocardium?
A2: Within first half hour of ischemia, no actual cellular death occurs. However, if blood flow is not restored, the myocardium undergoes waviness of fibers at the border, followed by coagulative necrosis in which cells form contraction bands, with hypereosinophilic dying cardiomyocytes and leakage of cardiac enzymes that are detected in the blood. In the first week inflammatory cells infiltrate the dying myocardium, first with neutrophils then followed by macrophages (slide C5). After about a week, granulation and fibroblasts begin replace the dead myocardium, followed in a couple of months by fibrosis with dense collagenous scar tissue (slide C7).

Q2: What are complications that can arise post-myocardial infarction (MI)?
A2: Depending on timing post-MI different complications can arise. Arrhythmia is the most common complication and can occur any time after MI, including atrial fibrillation and also ventricular tachycardia or fibrillation. Infarcted myocardium is at its weakest during period of neutrophil and macrophage invasion but well before fibrosis formation, typically within 2 weeks post-MI. Aneurysm of weakened myocardium and resulting thrombus formation is also a complication, albeit rarer than arrhythmias.

4) Abdominal aneurysm

A 71 year old man was brought into the emergency room for sudden loss of consciousness. He was accompanied by his daughter, who said that his father was complaining of severe abdominal pain just less than half an hour ago before suddenly feeling faint and falling down. Physical exam revealed blood pressure of 89/40.

Q1: What is the most likely diagnosis?
A1: Abdominal aortic aneurysm rupture (AAA) should be suspected in this case due to severe hypotension and abdominal pain before. Although many AAA cases are incidentally identified when the patient is having CT scan for another purpose, rupture of AAA presents with triad of abdominal pain, pulsatile abdominal mass, and severe hypotension. Mortality rate is high, and he should be transferred for emergency surgery.

Q2: What is the most common place for AAA formation, and how is AAA treated?
A2: AAAs mostly occur just below where renal arteries sprout from the abdominal aorta, and can involve parts of the renal arteries as well. Rupture risk increases proportionally to the size and rate of increase of the aneurysm. Current guideline states that asymptomatic AAA patients with aneurysm larger than 5 cm or growth faster than 4 mm/ year should undergo elective surgical intervention.

Q3: You see a patient in VA vascular surgery clinic, and ask about his smoking status, why?
A3: In addition to lung cancer and other diseases, smoking is associated with AAA formation and rupture.

Block 5: Pulmonary System II

1) Hamartoma

A 55 year old woman comes to the emergency room for sudden-onset palpitation and chest pain. During her cardiology workup, the ED also performed a chest x-ray, which revealed a single nodular opacity in her right upper lung field. After discharge, she was told to return to clinic for follow up of her lung findings.

Q1: Patient opted to have the lesion excised because she grew up with her parents who both smoked. Biopsy revealed the lesion to be hamartoma. What is commonly seen on a hamartoma?
A1: Hamartoma is a benign lesion, with abnormal tissue growth composed of well-differentiated cells appropriate for the location of the organ/tissue involved. For example, a pulmonary hamartoma is often composed of cartilage interspersed among fibrovascular stroma and bronchial glands.

2) Acute pneumonia

A 72 year old man with a history of stroke and congestive heart failure is admitted to the ED for shortness of breath and cough. He has not been feeling well for the past few days, and is now coughing up yellowish mucus and developing a fever. He has no sick contacts and his last hospitalization was 3 years ago for stroke. Physical exam revealed T 102, HR 99, BP 145/98, RR 22. His chemistry panel was within normal range and CBC revealed a WBC of 12.5. Chest radiograph showed right middle lobe consolidation and pneumonia was strongly suspected in addition to his clinical findings.

Q1: What kind of pneumonia is this?
A1: Pneumonia is divided into two (or more) groups based on setting in which it is acquired. Community-acquired pneumonia (CAP) is acquired by non-hospitalized patients. Hospital-acquired pneumonia (HAP) is acquired after 2 days of hospitalization. Healthcare-associated pneumonia (HCAP) is acquired in any healthcare setting such as dialysis unit, nursing homes, or any IV therapy or wound care within the last 30 days. There is also aspiration pneumonia from patient who cannot protect their airway. Pneumonia is divided into such categories due to pathogen differences and patients are often treated empirically before culture results come back. Common pathogens include *Streptococcus pneumoniae* for CAP, Gram negative rods such as *Pseudomonas* for HCAP, and anaerobes for aspiration. This patient likely has CAP because he has never been in any healthcare setting recently.

Q2: How does the lung parenchyma respond in pneumonia?
A2: Patches of alveoli may be infiltrated with neutrophils, with surrounding capillaries engorged with RBCs. In moderate or resolving pneumonia the alveoli architecture is preserved, and patient may return to full pulmonary function. In severe cases of pneumonia or abscess formation, alveolar walls can be destroyed.

3) *Pneumocystis jiroveci* pneumonia (formerly *Pneumocystis carinii*)

A 35 year old man comes urgent care for fever and cough. He says that the cough has been exacerbating for a few weeks. It has always been a dry cough, but lately a fever has also been developing. Review of systems revealed increasing fatigue and unintentional weight loss of 15 lb. over the last two months. Patient is a drifter and has history of IV drug use and risky sexual behavior. Physical exam revealed bilateral crackles at base. Chest radiograph showed bilateral diffuse ground glass opacification.

Q1: What is the next step?
A1: Patient's social history and unintentional weight loss and prolonged malaise raise the question of HIV infection, thus HIV ELISA and CBC with differential should be performed.

Q2: How does Pneumocystis pneumonia appear in specimens?
A2: *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) is a fungus and does not grow well in culture. Sputum induced by inhalation of saline is often the first step in diagnosis, followed by bronchoalveolar lavage if the former is inconclusive. Specimens are sent for cytopathology and GMS stain, a type of silver stain for fungal species. GMS would reveal cyst the size of RBCs, with black borders and one or two eccentric dots. They do not form hyphae like other yeasts. Cytology stains, cell block, and tissue biopsies or lung resections/autopsies may show foamy alveolar exudate containing cysts.

4) Small cell lung cancer

A 76 year old man comes to his primary care physician for cough with bloody sputum. He says that he has been having a dry cough for a few weeks now, but in the last few days he has been coughing up mucus with streaks of blood, which prompted him to this visit. Further history revealed that he started smoking as a teenager and only quit 5 years ago, and he has been having unintentional weight loss over the last year. A chest radiograph showed mediastinal widening and bilateral hilar opacities with normal appearing lung parenchyma. An excisional biopsy was performed, which revealed small cell lung cancer.

Q1: How does small cell lung cancer (SCLC) appear grossly, and what would microscopy show?
A1: SCLC is a "central" lung malignancy that is usually found as a perihilar mass with extensive necrosis and frequent nodal involvement. Within the lung, the tumor typically spreads along bronchi in a submucosal and circumferential fashion. The mass can also have a compressive effect causing collapse of distal lung or SVC syndrome. Histologically, tumor cells are found in nodules of small dark blue (hyperchromatic) cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli. The cells are round, oval, and spindle shaped. Nuclear molding is prominent. Necrosis is typically extensive and mitotic count is high.

5) Adenocarcinoma

A 50 year old woman comes to her primary care doctor for cough. She says that the cough has been developing for at least three months now, and within the last few weeks she has been coughing up minute amount of bloody mucus as well. She has never smoked, and review of

systems revealed increasing fatigue and shortness of breath for the past year that she thought was due to undergoing menopause. Chest radiograph showed a 3.5 cm lung nodule at the periphery of lower left lobe. A biopsy was performed, which indicated adenocarcinoma.

Q1: How is pulmonary adenocarcinoma present in location and patient risk factors?
A1: Lung adenocarcinoma most frequently arises from periphery of lung parenchyma rather than from central bronchi and their branches. Although most cases are seen in smokers, adenocarcinoma is the most common lung cancer type in non-smokers (particularly women).

Q2: How does pulmonary adenocarcinoma appear microscopically?
A2: Glandular differentiation or mucin production unites all adenocarcinomas. Glands may appear as lepidic, acinar, papillary, or micropapillary architecture, or as variants, ranging from relatively normal columnar cellular morphology to more disorganized or anaplastic appearance. Mucin can be found in intracellular globules or secreted outside, creating mucin-filled cysts. Adenocarcinomas appear in many tissues, but in lungs the word "lepidic" describes the growth pattern of pulmonary adenocarcinoma in which cancer cells grow along alveolar surface. Lung adenocarcinoma is subclassified based on a multidisciplinary approach, primarily based on histology, which may assist with choice of treatment, research protocols, and clinical trials.

6) Squamous cell carcinoma

An 80 year old man comes to his primary care provider for bloody sputum and cough. He has been having these symptoms for six months, and they seem to be getting worse. The patient is fairly certain that these are due to some underlying lung cancer because of his long smoking history. A chest radiograph showed left hilar enlargement and few nodular opacities in left lower lobe. A biopsy of hilar lymph nodes and nodules was performed and showed squamous cell carcinoma.

Q1: Where is squamous cell carcinoma usually located, and what is the most important risk factor?
A1: Squamous cell carcinoma usually develops from central bronchi and their branches, and consequently can cause post-obstructive bronchiectasis. Smoking is the most important risk factor for its development. Note that this is different from adenocarcinoma, which develops peripherally and although most cases are seen in smokers, is the most common lung cancer type in non-smokers (particularly women).

Q2: How does pulmonary squamous cell carcinoma appear histologically?
A2: Regardless of subtype, all squamous cell carcinomas are characterized by keratin production and presence of desmosomes. Squamous cells usually have distinct borders and hyperchromatic and polygonal nuclei. Keratin appears as bright pink material in H&E stains, and can form keratin pearls in well-differentiated and moderately-differentiated tumors. In addition, under high magnification, intercellular desmosomes acting as bridges between adjacent cells may be seen.

7) Coccidioidomycosis

A 35 year old man comes to his primary care clinic for annual visit. For the past year he has been doing fine, except that few months ago he had a bout of productive cough, chest pain, and low

grade fever. He didn't seek any medical help and that episode resolved in a few weeks. Review of systems indicated some intermittent mild pain in his knees, and fatigue on some days. He is a migrant worker and for the last six months he was working in construction in Arizona in dusty environments. The physician was suspicious of Valley Fever and ordered a chest radiograph, which showed a solitary nodule in his right middle lobe. The physician then ordered a blood test and sputum stain.

Q1: What could explain the patient's symptoms?
A1: A self-resolving pneumonia-like episode with lingering fatigue and sometimes migratory arthralgia is suggestive of a possible coccidioidomycosis given patient's mild disease course and working in an endemic area (Sonoran desert, central valley of California). In fact, most cases of coccidioidomycosis are subclinical. This patient liked inhaled arthroconidia in his construction work from contaminated dust/dirt.

Q2: How does coccidioidal infection appear in specimens?
A2: A respiratory secretion such as sputum or bronchoalveolar lavage may show fungal organisms. Culture can take weeks and may be negative. Fine needle aspiration cytology of lung mass under CT guidance may be diagnostic. H&E, Pap, and Diff-Quik stains may be sufficient, although GMS stain is the most sensitive test in detecting fungal species. A pathologist looks for endospores and particularly spherules, which are fungal spheres containing numerous endospores. These spherules develop from inhaled arthroconidia, and the spherules rupture and release endospores, which can cause more local infection or disseminated infection.

8) Miliary tuberculosis

A 37 year old man was brought by his friend for fatigue and periodic fever for the last month. Through his friend he says that he has been feeling unusually tired, with night sweats and coughs sometimes with bloody mucus. Review of systems uncovered many symptoms around the same time, including lower back pain, right upper quadrant abdominal pain, diarrhea, and unintentional weight loss. Patient was a recent immigrant from Mexico and does not smoke or drink alcohol. Physical exam revealed bibasilar crackles. Because of patient's symptom and recent immigration status, the attending suspected disseminated tuberculosis, and ordered serial acid fast stain of his sputum, quantiferon assay, and a chest radiograph in addition to the normal CBC and chemistry panels.

Q1: How does pulmonary tuberculosis appear grossly and histologically? What is miliary form?
A1: Pulmonary tuberculosis is marked by granulomas in the lung parenchyma that appear tan, mostly located in the upper lobes. Larger lesions may have central caseous necrosis. When a granuloma is near a bronchus, the central necrosis may be drained, leaving behind cavitation. Histologically these granulomas are composed of Langhans giant cells and a necrotic center. Langhans giant cells are fused epithelioid macrophages with multiple nuclei set to one side of the cell, and along with fibroblasts and other inflammatory cells, they wall off central necrotic debris and infection, which appears as pink proteinaceous material. When infection is particularly virulent or immune response is poor, the infection can disseminate to other parts of the body, and

the granulomas become smaller (2-4 mm) and diffuse in the lung parenchyma (miliary pattern, so named because of resemblance to millet seeds).

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