A Belly Full of Jelly

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**Learning Objective 1:** Identify the differential diagnosis of ascites without portal hypertension

**Learning Objective 2:** Understand the pathophysiology and clinical presentation of pseudomyxoma peritonei

**Case:** A 61 year-old man presented with several years of progressive abdominal and lower extremity swelling. The swelling had become profound in the past several weeks and he could barely ambulate. He denied a history of liver, cardiac, or kidney disease, or any drug use, transfusions, high-risk sexual behavior, or recent travel. The patient’s abdomen was markedly distended with ascites and a right-sided inguinal hernia was noted. He had 3+ pitting lower extremity edema to the thigh. No peripheral stigmata of liver disease or chronic alcohol use were found. His cardiac exam was normal with a normal jugular venous pressure. Laboratory studies revealed a serum albumin of 2.9 g/dL, with normal serum aspartate and alanine aminotransferases, alkaline phosphatase, creatinine, urinalysis, and coagulation studies. Studies for viral hepatitis were negative. Diagnostic paracentesis revealed yellow, thick, mucinous ascites with 411 leukocytes/mm³, 14% polymorphonucleocytes. The serum albumin-ascites gradient was 0.9 g/dL, indicating that portal hypertension was not likely present. Bacterial and mycobacterial cultures were negative. Fluid cytology and peritoneal biopsy were unremarkable. Computed tomography of the abdomen and pelvis with intravenous contrast revealed massive loculated ascites with small calcifications along septations. No masses or lymphadenopathy were noted. As the ascites was not likely due to hepatic, cardiac, renal, pancreatic, or infectious etiology, a mucin-producing neoplasm (pseudomyxoma peritonei) was suspected. Exploratory laparoscopy was performed. Fifteen liters of mucinous ascites were drained and a 38 x 20 x 11 cm mass originating from the appendix was discovered. A right hemicolectomy with end ileostomy was performed. Pathology revealed appendiceal mucinous adenocarcinoma. The patient declined chemotherapy. He remains alive two years after initial presentation.

**Discussion:** Ascites related to portal hypertension is commonly encountered by the internist, but cases without portal hypertension present a diagnostic challenge. Processes leading to ascites without portal hypertension include local or metastatic peritoneal carcinomatosis (most common), tuberculosis, pancreatitis, bile ascites, and chylous ascites from lymphatic system leakage.

Pseudomyxoma peritonei is a rare cause of ascites characterized by diffuse collection of gelatinous material from mucin-producing implants on peritoneal surfaces. Mucin-producing tissue can be either adenoma, termed disseminated peritoneal adenomucinosis, or adenocarcinoma, termed peritoneal mucinous carcinomatosis. Typically these neoplasms arise in the appendix. Peritoneal spread is thought to occur when an appendiceal neoplasm occludes the lumen of the appendix and ruptures it, seeding the peritoneum with mucin-producing cells. The abdomen slowly accumulates this mucinous ascites over months to years, leading to increased abdominal girth or a new inguinal hernia, the two most common presenting complaints of this condition. Computed tomography findings are often non-specific, but abdominal septations with calcifications raise the suspicion of this disease.

In conclusion, the presence of ascites without portal hypertension should prompt a broad differential diagnosis, and appendiceal tumors should be considered in cases of mucinous ascites.
The ART of Decreasing Cancer in the Hospitable Host

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Learning Objective 1: Recognize lymphoma as part of the differential diagnosis of a cardiac tumor in AIDS.

Learning Objective 2: Assess the likelihood of certain AIDS-defining malignancies based on the CD4 count.

Case: A 35-year-old man with HIV/AIDS (CD4 158, VL >4 million) presents with 2 weeks of progressive severe shortness of breath. His shortness of breath is confined to the supine position, without a decrease in exercise tolerance. He endorses anorexia, unintentional weight loss, low-grade fevers, and fatigue. His review of systems is otherwise negative. The patient was diagnosed HIV+ 10 years prior, but did not opt for treatment.

On admission the patient was afebrile and normotensive but tachycardic to 130 and tachypneic to 24, with oxygen saturation 97% on room air. Bilateral upper extremity edema and bilateral basal ronchi were noted. Chest X-ray showed bilateral pleural effusions. Echocardiogram showed pericardial effusion with tamponade physiology. CT thorax showed mediastinal adenopathy and a right atrial mass extending into the superior vena cava.

The pericardial effusion was drained and the mass endovascularly biopsied. Pericardial fluid cytology and biopsy were positive for non-Hodgkin’s Lymphoma (NHL), specifically Large B Cell Lymphoma. The diagnosis of Primary Effusion Lymphoma (PEL) was made based on the findings of pericardial effusion with HHV8+ immunoblastic B cell phenotype in an AIDS patient. Immediately after diagnosis, the patient began chemotherapy and has been clinically responsive thus far, with decreased shortness of breath and radiographic evidence of decreasing mass size.

Discussion: AIDS-defining malignancies including Kaposi’s Sarcoma, non-Hodgkin’s lymphoma and invasive cervical carcinoma were commonly seen in the pre-Antiretroviral Therapy (ART) era. The incidence of these malignancies has declined since the advent of ART and the consequent rise in patients’ CD4 counts, suggesting an inverse relationship between malignancy risk and CD4 count. Lymphoma subtypes found almost exclusively in AIDS are frequently associated with viruses, such as HHV8, which causes Primary Effusion Lymphoma. The reason for the high incidence of these infectious-driven cancers in HIV/immunodeficiency is thought to be the unchecked proliferation of HHV8 infected lymphocytes in the setting of T-cell deficiency.

PEL is defined as an immunoblastic HHV8+ B-cell lymphoma that presents as a pleural, peritoneal or pericardial effusion, traditionally without a coexisting solid tumor. Our patient presented with HHV8+ B cell lymphoma, PEL solid variant subtype, which is a recently recognized subtype, similar to traditional PEL, but associated with a mass. This is the second reported case of PEL presenting as a cardiac tumor and is the first reported case of PEL presenting as a right atrial tumor. The differential for our patient’s right atrial tumor was broad; atrial myxoma, metastasis, primary cardiac tumor, and thrombus were all considered given the location and clinical context. Although the prevalence of AIDS-defining Non-Hodgkin’s lymphoma has decreased in the era of HAART, it is important to keep PEL on the differential of a cardiac tumor in an HIV+ patient, particularly one with uncontrolled AIDS or HAART non-compliance. PEL generally has a poor prognosis; however the two reported cases of cardiac tumor PEL, including this case, improved rapidly with chemotherapy, rendering diagnosis very important.
A Curious Case of Recurrent Rhabdomyolysis

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Learning Objective 1: Identify the differential diagnosis of recurrent rhabdomyolysis.

Learning Objective 2: Describe a classic presentation and the treatment of McArdle disease in an adult.

Case: A 20-year-old male was admitted to our hospital for management of recurrent rhabdomyolysis. His first episode occurred when working as a firefighter extinguishing a house fire. The second instance followed a series of short-distance sprints, and his current presentation occurred after direct trauma to his legs. Each episode was characterized by myalgias, followed by morning stiffness, and dark urine lasting several days. He also reported a life-long history of exercise intolerance with easy fatigability. He was diagnosed with diabetes mellitus four months prior to admission and was briefly treated with metformin, which was later discontinued in favor of insulin due to intolerance. He also experienced an episode of ventricular tachycardia at the age of 15 for which he underwent an ablation. His family history was notable for his mother and a maternal uncle with dermatomyositis and a maternal uncle with an undifferentiated myositis. The patient denied any alcohol, tobacco, or drug use. Physical exam revealed a tired-appearing young man in no acute distress. He was afebrile with normal vital signs. Cardiac, lung, abdominal and dermatologic exams were unremarkable. Musculoskeletal exam revealed 5/5 strength throughout, with no joint tenderness, swelling, or deformity. Labs revealed a CPK 78,465, LDH 2657, AST 492, ALT 272, Alk Phos 61, Tbili 0.9. A basic metabolic panel and CBC were unremarkable. A TSH was normal. CRP was 1.9. RF, ANA, and Anti-JO-1 Abs were also negative. A cytogenetic analysis was ultimately performed, revealing mutations in two exons of the PYGM gene encoding the myophosphorylase enzyme. This was consistent with McArdle disease.

Discussion: Rhabdomyolysis is a common clinical entity encountered by general internists. It is frequently caused by direct trauma, hyperthermia, infection, or exposure to toxins and drugs. When recurrent rhabdomyolysis is identified, it is important to investigate for underlying inflammatory and metabolic etiologies, such as dermatomyositis, polymyositis, and inclusion body myositis, in addition to the family of glycogen storage diseases. McArdle disease is a glycogen storage disease caused by mutations in the myophosphorylase enzyme. Patients often present as teenagers or young adults with exercise intolerance, fatigue, myalgias, muscle cramps, and myoglobinuria. Common diagnostic tools include muscle biopsy, electromyography, genetic testing, and forearm lactate exercise testing. Muscle biopsy shows focal decreased myophosphorylase activity on immunohistochemical staining. Electromyography demonstrates myotonic discharges, fibrillations, and positive waves. Genetic testing of the myophosphorylase gene reveals mutations in approximately 97% of McArdle disease patients. Treatment of McArdle disease includes sucrose administration prior to dynamic exercise with low-impact warm up activity and a balanced diet of carbohydrates, protein, and fat. Other potentially beneficial therapies include creatinine and vitamin B6 supplementation. For our patient, given his family history and recurrent nature of rhabdomyolysis, further investigation of potential genetic disorders and inflammatory myopathies yielded a definitive diagnosis of McArdle disease.
Learning Objective 1: Understand the importance of taking a detailed history of ingestion of over the counter herbal supplements.

Learning Objective 2: Recognize the association between acute hepatitis and ingestion of over the counter cinnamon supplement.

Case: A 42 year-old man with history of diabetes mellitus presented with a 2-day history of 9/10 throbbing abdominal pain, nausea and diarrhea. The pain was initially localized to the peri-umbilical region but later migrated to the right upper quadrant. He denied prior diagnosis of hepatitis, intravenous drug or acetaminophen use, but acknowledged occasional alcohol intake. His only medication was 1000 mg of twice daily metformin and he had no family history of autoimmune disease. Upon further questioning, he reported a 2-week consumption of the over the counter herbal cinnamon pills “to help” with his diabetes. He had right upper quadrant tenderness with a palpable liver edge 5cm below the right costal margin. Abnormal admission labs included an AST of 969 U/L, an ALT of 724 U/L, an alkaline phosphatase (ALP) of 155 U/L and a total bilirubin of 1.3 mg/dL. Other laboratory values including amylase, lipase, anti-nuclear antibodies and INR were within normal limits and an acute viral hepatitis panel and HIV test were negative. Abdominal ultrasound revealed hepatomegaly with fatty infiltration. He was advised to discontinue the herbal cinnamon supplements and by hospital day 4 his abdominal pain had resolved with AST/ALT and ALP levels decreasing to 319, 447 and 99 U/L, respectively. Three weeks later, liver enzymes returned to normal (AST 40, ALT 40, ALP 65 U/L) and a repeat hepatitis panel was non-reactive. A repeat abdominal ultrasound showed diminished hepatomegaly with resolution of the fatty infiltrates.

Discussion: The general internist should be aware that the use of over the counter herbal supplements has rapidly grown in popularity during recent years. Use of cinnamon, in particular, has risen amid recent reports of its ability to decrease blood glucose, serum triglyceride and low-density lipoprotein levels. While the benefit of cinnamon supplementation may be real, unfortunately many herbal supplements are not composed of pure cinnamon. Rather they contain cassia cinnamon, which is known to have substantially larger quantities of a potentially toxic substance, coumarin. Whereas regular cinnamon contains low levels of coumarin (0.5% and under), cassia cinnamon can contain up to 5% coumarin. Approximately 20 cases of coumarin-induced hepatitis have been documented in the past 20 years, with occurrence following both long term (>2 years) and short term (<3 weeks) ingestion. Resolution of hepatitis with a return to normal transaminase levels has been reported to occur within 4-8 weeks following discontinuation of cinnamon supplementation. As herbal supplements and other “organic” substances become increasingly popular, the importance of obtaining a detailed history of over-the-counter medication use cannot be overstated. It is important to keep in mind that “natural” does not necessarily mean “harmless.”
Fevers, rash and joint pain, Still?

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Learning Objective 1: Recognize the clinical presentation of Adult-Onset Still’s Disease (AOSD)

Learning Objective 2: Understand the diagnostic criteria for AOSD.

Case: A 32 year-old woman presents with two weeks of intermittent fever, nonpruritic rash, and migratory polyarthritis with effusions. She initially presented with a fever of 103°F, myalgias, and erythematous, blanching rash on bilateral thighs, arms, and dorsum of feet and hands. Review of systems was positive for rhinorrhea, sore throat, hyperalgesia and migratory polyarthritis of knees, wrists and ankles. She denied insect bites or sick contacts. Initial exam was nonfocal, notably without fever, lymphadenopathy, rashes or hepatosplenomegaly. During hospitalization, she had quotidian fevers often accompanied with macular rash and migratory large-joint effusions. Laboratory workup was notable for leukocytosis of 11.3, alkaline phosphatase of 153, AST of 49, ALT of 60 (previous lab results had normal LFTs), ESR of 92 and CRP of 12.9, but negative for viral and bacterial illnesses. Imaging was negative for malignancy. Initial ferritin level was 450, but was repeated on hospital day four and found to be 991. A diagnosis of Adult-Onset Still’s Disease was made and the patient was started on prednisone with resolution of fever, rash and joint pain. As an outpatient, she was tapered off of steroids due to side effects and has remained symptom free three months after diagnosis, with normal ferritin levels.

Discussion: Adult-Onset Still’s Disease (AOSD) is an inflammatory condition characterized by intermittent fevers, rash and polyarthritis. First described in 1897 by George Stills as systemic onset juvenile idiopathic arthritis, AOSD was recognized in adults that do not fit the criteria for rheumatoid arthritis but have similar clinical presentations accompanied with fever. Though pathophysiology is unclear, it has been suggested that alterations in cytokine production (particularly Th1 cytokines) play an important role in the development of AOSD, and may be triggered by various infectious agents and stress. While no specific laboratory, imaging or clinical criteria confirm the diagnosis, the Yamaguchi criteria are most widely used, with a sensitivity of 93.5% when five features (at least two major criteria) are present. Major criteria include fever >102.2 for >1 week, arthralgias/arthritis >2 weeks, non-pruritic macular, salmon-colored rash (usually during fever), leukocytosis >10,000 (>80% granulocytes). Minor criteria are sore throat, lymphadenopathy, hepatomegaly or splenomegaly, abnormal LFTs, negative ANA and RF. Elevated ESR and CRP are present in almost all cases, and elevated ferritin (>1000) is seen in up to 70% of patients. Total ferritin and glycosylated fraction can be useful in ruling out other rheumatological processes. Normally, 50-80% of ferritin is glycosylated. In AOSD, the fraction decreases due to a saturation of glycosylation mechanisms and a glycosylated ferritin fraction <20% has specificity of 93% for AOSD. The clinical course of AOSD generally follows three patterns: monophasic (with complete resolution of symptoms within one year), intermittent (with episodic flares), and chronic (with persistently active disease often associated with destructive arthriti). Similar to other inflammatory arthritides, treatment for AOSD includes NSAIDS, glucocorticoids (required in most patients), and antirheumatic agents. DMARDS are often utilized in refractory cases, despite lack of controlled-trials demonstrating efficacy.