REFRACTORY HYPOGLYCEMIA IN A TYPE 1 DIABETIC PATIENT - CLUE TO ADDISON'S DISEASE AND AUTOIMMUNE POLYENDOCRINE SYNDROME TYPE 2
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LEARNING OBJECTIVE 1:
Recognize features of Autoimmune Polyendocrine Syndrome type 2 (APS-2).

LEARNING OBJECTIVE 2:
Manage and appropriately screen APS-2 patients.

CASE:
A 47-year-old Caucasian female presented for the third time to the emergency room with hypoglycemia and hypotension. For 3 months, she had recurrent hypotension, hypoglycemia, fatigue, orthostatic dizziness, weight loss and vomiting. She had a 16-year history of T1DM. Glycemic control was stable for 6 years on same dose of insulin. She had hypothyroidism for 5 years, also stable on levothyroxine. She denied recent travel, lifestyle or medication changes. Insulin dose was adjusted several times but hypoglycemic episodes persisted, occurring 2-3 times weekly. For her symptoms, she had seen a Cardiologist, Neurologist, Otorhinolaryngologist, Primary Care and Emergency Physicians. Work up thus far excluded Multiple Sclerosis, cobalamin deficiency, myasthenia gravis, hemochromatosis, vestibular, cardiac and rheumatologic disease. On examination she was alert and oriented, hypotensive; Blood Pressure=87/53mmHg and tachycardic; Heart rate=124/min. Her skin was diffusely tan. The remaining exam was unrevealing. Labs showed Complete Blood Count, renal, liver and thyroid function tests were within normal range. Blood glucose was 70mg/dl. Adrenal insufficiency was suspected based on hypoglycemia, hypotension, tachycardia and tan skin. This was confirmed with serum cortisol = 0.8mcg/ml (normal 8.7-22.4mcg/dl) and ACTH = 298pg/ml (normal 10-60pg/ml). After intravenous hydrocortisone and fluids, symptoms resolved. Given hypothyroidism, adrenal insufficiency and T1DM further antibody tests confirmed APS-2.

DISCUSSION:
APS-2 is an autosomal dominant disease affecting HLA genes. APS-2 is characterized by Addison's disease, autoimmune thyroid disease and type I diabetes mellitus. Other associated disorders include Pernicious anemia, celiac disease, Hepatitis, Hypogonadism, Hypophysitis, vitiligo. Unlike APS-2, APS-1 affects only children. APS-2 occurs more in females and is often diagnosed between ages 30s to 40s. Although APS-2 is uncommon (1.4-4.5 per 100,000), its prevalence increases when subclinical cases are included (150 per 100,000) implying it is not as rare as believed. The clinical presentation depends on specific APS-2 component disorders and involved organs. However, conventional treatment for each component disorder is often sufficient. Specialist care is required only as needed. The importance of APS-2 is illustrated in our patient. More than one APS-2 disorder should raise vigilance for associated disorders given that clinical features of these disorders are nonspecific. In addition, the interval between development of one disorder and the next can be as long as 20years, making screening necessary for early initiation of disease-specific management. Experts recommend that patients with two APS-2 disorders should be screened every 1-2 years until 50years old. In addition to detailed history and physical examination, screening includes autoantibody testing for T1DM, thyroid disease, Addison's disease, Celiac disease and autoimmune hepatitis. Vitamin B12, sex hormone and blood glucose levels including liver and thyroid function tests are also useful.
LEARNING OBJECTIVE 1:
Acute Cholecystitis can present with EKG changes suggestive of Myocardial Ischemia, usually as ST depression but very rarely ST elevation as well.

LEARNING OBJECTIVE 2:
Importance of using clinical judgement when dealing with ambiguous clinical presentation to avoid anchoring bias.

CASE:
A 53 year-old Caucasian male with a past medical history of diabetes, dyslipidemia, extensive smoking and family history of cardiac disease, presented with acute-onset midsternal pressure-like chest pain that had awakened him from sleep. There was also associated vague right upper quadrant abdominal pain and nausea. Physical examination was normal, except right upper quadrant abdominal tenderness. The white blood cell count was 13,600 per microliter. Initial EKG revealed diffuse ST segment elevation in leads I, II, III and V3-V6, along with peaked T waves in V3 and V4; two sets of troponins were negative. He was given intravenous nitroglycerin which provided moderate pain relief. An emergent cardiac catheterization was negative for focal obstructive coronary artery disease. Simultaneously he was started on intravenous antibiotics for suspected cholecystitis, which was confirmed by pericholecystic fluid seen on gallbladder ultrasound as well as by HIDA scan. The patient underwent laparoscopic cholecystectomy two days later, and was found to have acute on chronic gangrenous acalculous cholecystitis. Post-operatively, follow-up EKG's revealed near normalization of the ST segment changes.

DISCUSSION:
Acute cholecystitis is usually recognized by a triad of fever, leukocytosis and right upper quadrant pain. The two main types are calculous and acalculous cholecystitis. There have been multiple references to acute cholecystitis presenting with EKG changes such as T wave inversions or ST segment depressions, but there have only been a handful of instances where ST-segment elevation was present. The exact pathophysiology of the EKG changes in acute cholecystitis is unclear. Based on animal experiments, a possible relationship of gallbladder distension to increased heart rate, blood pressure and plasma renin levels has been postulated to cause transient changes in the coronary vasculature. In our literature review, we found 8 previous case reports of ST-segment elevation in patients with cholecystitis. Of these 8 cases, there was only one reference to acalculous cholecystitis while the rest were associated with gallstones. Our case reiterates the importance of exercising appropriate clinical judgment in the face of ambiguous findings. Having knowledge of this "red herring" in patients with cholecystitis could prevent unnecessary diagnostic testing and ensure timely administration of antibiotics as well as prompt surgery, if indicated.
A YOUNG WOMAN WITH CHEST PAIN AFTER A SORE THROAT AND FEVER

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LEARNING OBJECTIVE 1:
Recognize the features of carditis in acute rheumatic fever

LEARNING OBJECTIVE 2:
Recognize the diagnostic error of premature closure

CASE:
A 33 year old woman with no significant medical history was admitted at this hospital with diffuse chest, abdominal, and back pain. Two weeks prior to presentation, the patient had had a sore throat with fever. These symptoms resolved after one week. Five days prior to presentation, the patient developed severe abdominal, chest, and back pain associated with fever, chills, and rigors. The pain was diffuse and often pleuritic. She took large doses of ibuprofen, up to 800 mg four times daily, with minimal improvement in symptoms. She was prescribed azithromycin at an urgent care center one day prior, but her symptoms persisted and she presented at the Emergency Department for further evaluation. On presentation, the patient was afebrile, tachycardic to 102 beats per minute, tachypneic to 26 breaths per minute, and normotensive. Her physical examination was otherwise normal. A complete blood count was remarkable for a leukocytosis of 23,400. Her serum creatinine was 5.89 mg/dL. The serum level of troponin I was 4.28 ng/mL. EKG showed normal sinus rhythm with no ST depressions or elevations. Urine toxicology screen was negative for all tested substances. Serum CRP was 10.95 mg/dL. ASO titer was elevated to 687 IU/mL (normal is < 144 IU/mL). Throat culture was negative for Streptococcal species. Blood culture was positive for Streptococcus pyogenes. Accounting for her history of a sore throat and a positive streptolysin titer, the patient was diagnosed with acute rheumatic fever based on 1 major Jones criterion (carditis) and 2 minor Jones criteria (history of fever and elevated CRP). An echocardiogram was normal and showed no significant valvular disease. Her acute kidney injury was attributed to NSAID nephrotoxicity and resolved with intravenous fluids. The patient was initially treated with vancomycin, piperacillin-tazobactam, and penicillin VK, then subsequently narrowed to amoxicillin-clavulanate. Her pain was treated with ibuprofen and hydromorphone. She was discharged on the fifth day of her hospitalization with instructions to complete a 14-day course of amoxicillin-clavulanate. Two days after discharge, the patient returned to the Emergency Department with severe pleuritic back and chest pain. A chest X-ray was abnormal with a new opacification of the right lower lobe concerning for collapse. CT of the chest revealed an empyema of the right posterior thorax. The patient's diagnosis was revised from acute rheumatic fever to streptococcal toxic shock syndrome from empyema. The patient subsequently underwent video-assisted thoracoscopic surgery for drainage and lung de-cortication. After a 14 day course of IV antibiotics, the patient made a full recovery.

DISCUSSION:
The misdiagnosis in this case resulted in part from a misunderstanding and misapplication of the Jones criteria for the diagnosis of acute rheumatic fever. On physical examination and on echocardiographic imaging, the patient did not have any evidence of the valvular injury that is characteristic of carditis from acute rheumatic fever. In the absence of valvulitis, the patient was unlikely to have acute rheumatic fever. Moreover, it was incorrect to attribute the patient's pain symptoms and elevated serum troponin to rheumatic carditis, and premature closure prevented a search for alternative etiologies. In retrospect, the patient had low pre-test likelihood for acute rheumatic fever because initial attacks of acute rheumatic fever are rare in adults. Her history of sore throat two weeks prior to hospitalization was ultimately a red herring. A series of cognitive errors resulted in the failure to recognize and treat the correct diagnosis in this case, streptococcal toxic shock syndrome.
LEARNING OBJECTIVE 1:
Recognize primary coccidioidal infection after treatment failure for community acquired pneumonia.

LEARNING OBJECTIVE 2:
Awareness of the anchoring heuristic.

CASE:
A 31-year-old man presented with 1 day of left-sided pleuritic chest pain. Lungs were clear to auscultation without wheezes, rales, or rhonchi. On chest x-ray the patient had a left lower lung airspace consolidation, and he was given doxycycline for treatment of community-acquired pneumonia (CAP). The patient subsequently developed cough, fevers, and chills despite taking the doxycycline. He returned one week later and chest CT revealed a consolidation with a confluent focus in the lingula with scattered groundglass and centrilobular nodules, a small left pleural effusion, left hilar lymphadenopathy, and no pulmonary embolism. The patient was diagnosed with a non-resolving pneumonia and started on levofloxacin. He returned 4 days later with continued pleuritic chest pain, cough, malaise, and nightsweats. The patient declined hospital admission citing a personal obligation. He was given one dose of ertapenem with the plan to follow-up the next day. On follow-up, he had multiple painful nodules on the right shin consistent with erythema nodosum. Upon further questioning, he revealed that he had participated in a "Tough Mudder" endurance race near San Diego one week prior to symptom onset. He was admitted, started on fluconazole for presumed primary coccidiodal infection, and discharged after a brief hospital stay. Cocci antibody complement fixation was eventually positive with a titer of 1:4 and cocci ELISA was also positive, confirming the diagnosis. The patient was seen in follow-up one week after initiation of therapy with much improvement in symptoms.

DISCUSSION:
Pleuritic chest pain, cough, and fevers are common problems encountered in outpatient medicine. The presence of an infiltrate on chest x-ray is the gold standard for diagnosis of pneumonia. The decision to treat with antibiotics as an outpatient is based on a multitude of factors including the history, physical exam, laboratory values, and psychosocial situation. It is important to be aware of the anchoring heuristic, the clinging to an original diagnosis despite evidence to the contrary, when treating common, nonspecific symptoms as an outpatient. One should consider alternative diagnoses when a patient fails to respond to treatment as expected. Primary coccidioidal infection is a common cause of CAP in endemic areas. There is a spectrum of presentations, many of which do not require treatment. In our patient, alternative diagnoses were pursued when the patient failed appropriate therapy for a bacterial pneumonia and developed erythema nodosum. Careful attention to the patient's social, travel, and exposure history revealed clues about exposure to cocci during the outdoor race in an endemic area, which if elicited during a prior visit, may have led to an earlier diagnosis. The consideration of non-bacterial causes of pneumonia coupled with the compelling exposure history enabled a diagnosis of primary coccidioidal infection. The decision to treat was based on symptom severity (debilitating enough to keep patient out of work) and proximity to meeting two treatment criteria (>3 weeks of nightsweats and prominent hilar lymphadenopathy). Initiation of therapy with fluconazole resulted in improvement in the patient's symptoms. Coccidiomycosis is a common cause of CAP in endemic areas. Physicians should be mindful of the anchoring heuristic and actively seek out alternative diagnoses when patients do not respond to empiric therapy for a presumed bacterial pneumonia.

A fifth vignette will be presented using the “Unknown” format. Therefore, it is not included here.