LITHIUM-INDUCED HYPERTHYROIDISM MIMICKING ACUTE CORONARY SYNDROME

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LEARNING OBJECTIVE 1:
Diagnose and treat hyperthyroidism-induced coronary vasospasm in acute chest pain presentation.

LEARNING OBJECTIVE 2:
Recognize the various thyroid dysfunctions that can result from lithium use, even at subtherapeutic levels.

CASE: A 50-year-old female with chronic obstructive pulmonary disease, tobacco use and bipolar disorder presented with acute, intense substernal chest pain and heart rate of 170 bpm. She had no previous cardiac history and no similar episodes in the past. She started taking lithium 2 months earlier for bipolar disorder. Her electrocardiogram showed inferior ST depression and an incomplete left bundle branch block (LBBB). Troponin T was elevated at 0.48 ng/mL. An emergent left heart catheterization revealed non-obstructive coronary artery disease and vasospasm of the left main and left anterior descending coronary arteries which resolved with intra-coronary nitroglycerine. She remained tachycardic and the electrocardiogram later showed multifocal atrial tachycardia. A subsequent thyroid-stimulating hormone level came back low (< 0.01 mIU/L) and free T4 elevated (3 ng/dl). Thyroid stimulating antibodies were negative however thyroid peroxidase (TPO) was positive. Thyroid ultrasound was unremarkable. Despite a sub-therapeutic lithium level (0.53 mmol/L), lithium-induced hyperthyroidism was suspected given its narrow therapeutic index. Lithium was discontinued and methimazole was started. After 2 days, she became asymptomatic and converted to normal sinus rhythm; she was discharged with cardiology and endocrinology follow-up.

DISCUSSION: The presentation of severe coronary artery spasm can be similar to acute coronary syndrome (ACS). Unlike ACS, coronary artery spasm is more easily reversible and can be prevented by treating underlying causes. Coronary artery spasm is part of variant angina and if left untreated, can lead to myocardial infarction by promoting coronary thrombus formation. Furthermore, coronary artery spasm can cause life-threatening arrhythmias including heart block (with right coronary artery spasm) or ventricular tachycardia (with left anterior descending coronary involvement). Coronary vasospasm has been reported in patients with overt hyperthyroidism. The management generally includes thionamides (methimazole or propylthiouracil) to treat the hyperthyroid state as well as long-acting nitrates or dihydropyridine calcium channel blockers to decrease spasm of the coronary arteries. Interestingly, lithium itself is also used to treat hyperthyroidism by blocking thyroid hormone release, although its use is certainly not first or second line. There is little in the medical literature regarding coronary vasospasm secondary to hyperthyroidism as evidenced by a review of 21 case reports describing this clinical scenario. Of these 21 cases, 14 were attributed to Graves' disease (67%), 2 to toxic multinodular goiter (10%), 1 to amiodarone-induced hyperthyroidism (5%) and the remaining cases did not provide the underlying etiology for the hyperthyroidism. This patient may have been in "Hashimototoxicosis" (initial hyperthyroid phase of Hashimoto's disease) as evidenced by positive TPO antibodies and may eventually become hypothyroid due to underlying chronic autoimmune thyroiditis, with a predisposition for autoimmunity secondary to lithium. One study found that 20% of lithium-treated affective disorder patients had elevated TPO antibodies vs. 7.5% in non-lithium treated patients and 0% in controls. Lithium has a narrow therapeutic index and can cause thyroid dysfunction (hypo or hyperthyroidism) even at sub-therapeutic levels. A particular case series showed a 3-fold increase of thyrotoxicosis in patients taking lithium. Lithium use has also been associated with a self-limited destructive thyrotoxicosis (lithium-associated thyroiditis). This particular type of hyperthyroidism falls under the category of subacute painless thyroiditis and typically resolves over the course of months to years with adequate treatment of the hyperthyroid state. In conclusion, this case highlights key points in the diagnostic evaluation of acute chest pain. First, non-ST elevation myocardial infarction or new LBBB do not establish a diagnosis of a type 1 myocardial infarction (secondary to acute plaque rupture) but could be secondary to acute coronary vasospasm (type 2 myocardial infarction; secondary to decreased oxygen delivery or increased oxygen demand). Second, hyperthyroidism must be considered with chest pain presentations, especially in patients with low Framingham risk score and isolated coronary artery vasospasm on heart catheterization. Finally, thyroid function should be evaluated in all patients who take lithium, given its narrow therapeutic index.
THE UNUSUAL SUSPECT: PARANEOPLASTIC MONONEURITIS MULTIPLEX

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LEARNING OBJECTIVE 1:
Include paraneoplastic syndrome in the differential diagnosis of mononeuritis multiplex.

LEARNING OBJECTIVE 2:
Recognize that mononeuritis multiplex can precede any other manifestation of a primary malignancy.

CASE: A 44 year old Caucasian man presents with acute lower back pain for 2 days. He has a history of a recent left orchitis and epididymitis treated with antibiotics, and multiple cranial nerve palsies and mononeuritis multiplex of unknown etiology that had persisted for 3 years. His previous symptoms had included left sixth and third cranial nerve palsies and unilateral, intermittent limb pain. He had previously undergone an extensive work up for rheumatologic, metabolic, toxic, and neoplastic etiologies, which was negative. Cerebrospinal fluid analyses were normal. Electromyography showed a right ulnar nerve focal neuropathy. A sural nerve and muscle biopsy showed mild axonal degeneration and chronic neurogenic changes, respectively. Numerous MRI and CT scans of his head and spine were unremarkable. A whole body gallium 67 imaging study was negative. Anti-hu antibody was negative. His neurologic symptoms were treated with intermittent steroids. On presentation, his exam was notable for anisocoria (left pupil larger than the right) with impaired adduction of the left eye, decreased light touch sensation on both sides of the forehead, and 3/5 strength in right hip flexion and ankle dorsiflexion. He had a palpable, non-tender left testicular nodule. Labs were only notable for new thrombocytopenia, with a platelet count of 37,000. A spine MRI with contrast showed new enhancement of the conus medullaris that was concerning for leptomeningeal involvement of a malignancy. A brain MRI now demonstrated a new left cavernous sinus mass. He underwent a bone marrow biopsy, which revealed a diffuse large B-cell lymphoma. He also underwent a left orchiectomy, and pathology showed a primary testicular lymphoma. PET/CT scan showed scattered lymph nodes as well as lesions in the spleen, thyroid, adrenal gland, and skeleton that were hypermetabolic and consistent with metastatic disease. The final diagnosis was primary testicular lymphoma, diffuse large B-cell type, with CNS and bone marrow involvement, and paraneoplastic mononeuritis multiplex. His neurologic symptoms improved dramatically after initiation of chemotherapy.

DISCUSSION: Involvement of the peripheral nervous system occurs in 5\% of lymphoma cases, mostly in non-Hodgkin lymphomas. Neuropathy in lymphomas is either a result of neurolymphomatosis (i.e. direct invasion of lymphoma cells into the peripheral nervous system, which is diagnosed pathologically or by positive signals on PET imaging) or a paraneoplastic syndrome, which is much less common. This case illustrates mononeuritis multiplex as the initial presentation of lymphoma, preceding the lymphoma diagnosis by several years. Malignancy was included in the differential during his prior work up, but was never proven until this presentation. Ultimately, his mononeuritis multiplex was attributed to a paraneoplastic disorder based on nerve biopsies and PET scans that failed to show direct lymphoma involvement of the peripheral nerves, as well as the fact that his symptoms resolved after chemotherapy. References 1. Hughes RA, Britton T, and Richards M . Effects of lymphoma on the peripheral nervous system. J R Soc Med. 1994 September; 87(9): 526-530. 2. Tomita M, et al. Clinicopathological features of neuropathy associated with Lymphoma. Brain 2013: 136; 2563-2578
LEARNING OBJECTIVE 1:
Recognize that amiodarone pulmonary toxicity (APT) can occur any time after commencement of amiodarone and it is a diagnosis of exclusion

LEARNING OBJECTIVE 2:
Recognize the increased risk of acute APT following lung resection

CASE:
An 80-year-old male with a 15-pack-year cigarette smoking history and coronary artery disease underwent a right upper lobeectomy for lung adenocarcinoma (T2A N0 M0, Stage 1b). Preoperative transthoracic echocardiography (TTE) showed normal left ventricular function. Preoperative pulmonary function tests (PFTs) revealed a forced expiratory volume in 1s (FEV1) of 2.19L (71% of predicted), forced vital capacity (FVC) of 2.86L (71% of predicted), FEV1/FVC ratio of 77%, total lung capacity (TLC) of 4.45L (66% of predicted) and a diffusion capacity for carbon monoxide (DLCO) of 13.5mL/mmHg/min (59% of predicted). Postoperative (postop) course was complicated by subcutaneous emphysema which necessitated prolonged intubation. On postop day 4, he developed paroxysmal atrial fibrillation with rapid ventricular rate and was loaded with IV amiodarone for rhythm control at a rate of 0.5 mg/min which was then converted to 400mg tid orally on postop day 8. He was transferred to a rehabilitation center on postop day 12 in a relatively stable condition. On postop day 15, patient presented to the hospital with severe dyspnea, dry cough and syncope. He denied chest pain, diaphoresis, nausea or fever. He had received a total dose of 12.5g amiodarone in the preceding 12 days. There were no known environmental exposures. On physical examination, patient had diffuse dry crackles and no wheezes. Neck veins were not distended and there was no pedal edema. Arterial blood gas showed hypoxemia without CO2 retention. Cardiac enzymes were normal and there were no EKG changes. Laboratory studies showed a leukocytosis and elevated ESR. Chest CT scan revealed bilateral airspace opacities and mediastinal adenopathy. ACE level was normal and collagen vascular work up, including ANA, RF and ANCA, was negative. Blood culture did not grow any organisms. Postop PFTs revealed a severe restrictive disease: FEV1 of 1.24L (41% of predicted), FVC of 1.61L (39% of predicted), FEV1/FVC ratio of 81%, TLC of 3.13L (42% of predicted) and DLCO of 6.5 mL/mmHg/min (24% of predicted). TTE showed normal valvular and left ventricular function with elevated pulmonary artery (PA) pressure (80 mmHg). Cardiac catheterization which was done seven months ago had shown normal PA pressure. Amiodarone was discontinued and he was started on prednisone due to suspicion for APT. He improved symptomatically and radiographically, however he was still requiring 3L of intranasal oxygen. He was discharged home on oxygen and was placed on one month prednisone taper. On postop day 52 (four days after completing steroid therapy), he again presented to the hospital with similar complaints of severe dyspnea with high oxygen requirements. Radiological findings were improved but not back to baseline. He underwent bronchoscopy which revealed normal bronchial mucosa. Bronchial washing cytology was negative for AFB or malignancy and there was no growth on culture. Microbiologic analysis of bronchial washing showed a neutrophilic leukocytosis. Clinically, he improved and he was discharged on a prolonged course of prednisone.

DISCUSSION:
APT is the most severe adverse effect associated with the use of amiodarone. Pulmonary fibrosis following APT is irreversible, therefore anticipation and early detection of this potentially fatal side effect is important. Onset of APT has usually been observed after several months or years of amiodarone use. In the above case and a handful of other cases reported in literature, pulmonary toxicity can occur within a few days to weeks. The clinical findings in APT are non-specific and it remains a diagnosis of exclusion. The diagnosis of APT needs to be considered in high risk patients on amiodarone irrespective of dose, presenting with new or worsening respiratory symptoms or signs, new chest radiographic abnormalities or a decline in DLCO > 20%. Risk factors in our case include old age, pre-existing lung disease, thoracic surgery, intubation and amiodarone dose ≥ 400 mg/day. In a subset of patients undergoing thoracic surgery who are intubated and require high levels of oxygen, it has been postulated that the risk of developing APT is further heightened due to increased susceptibility for lung damage. Studies on risk factors for APT development have not been conclusive, however, in patients with multiple risk factors, there needs to be a discussion on the risks and benefits of amiodarone treatment. Finally, management of APT requires discontinuation of amiodarone and commencement of steroids for greater than six months. As in the case presented, tapering steroids too early may lead to symptom recurrence.
THE PERFECT STORM: A FEBRILE ANAPHYLACTOID REACTION

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(Tracking ID #1927138)

LEARNING OBJECTIVE 1:
Distinguish anaphylactoid reactions from IgE mediated anaphylaxis.

LEARNING OBJECTIVE 2:
Recognize a novel association of mast cell degranulation and fever in the setting of granulocyte colony stimulating factor

CASE:
A thirty year old female with BRCA-1 and triple negative bilateral breast cancer presented with a fever and rash. She previously had a bilateral mastectomy, radiation, and recently completed her third cycle of docetaxel and cyclophosphamide nine days prior to admission. Eight days prior, she received pegylated granulocyte colony stimulating factor (G-CSF). Cephalexin was prescribed over the phone for bilateral arm swelling that turned out to be lymphedema. She tolerated her first dose, but woke four hours after the second dose of cephalexin with a diffuse pruritic rash. In the ER, her temperature was 38.0, heart rate 132 and blood pressure 86/47. Her extremities and torso exhibited erythematous, well circumscribed, raised plaques with central pallor consistent with urticaria (image available for presentation). There was no stridor or wheezing. Four hours later she developed angioedema of her lips, sparing her tongue. These symptoms quickly resolved with IM epinephrine, IV fluids, diphenhydramine, and methylprednisolone. She had a recurrence of her angioedema on hospital day 2 that again improved with IM epinephrine. Prior to corticosteroids, the WBC was 30,000 with 92% neutrophils. Without any significant course of antimicrobials, the WBC normalized by hospital day 3. The patient spiked nightly fevers that were associated with flares of urticaria until hospital day 4. Penicillin skin testing done at the bedside was negative. An infectious work up was negative including repeated blood and urine cultures, stool C. Difficile PCR, serum CMV PCR, monospot, and nasal respiratory viral PCR. CT of the chest, abdomen and pelvis was unrevealing other than pericholecystic fluid with a normal HIDA scan. Ultrasound of the four extremities was negative for DVT. The patient was discharged on hospital day 5. She has since completed several more cycles of chemotherapy without further complications.

DISCUSSION:
The differential for a rash and fever is broad. Infectious etiologies are possible, though her extensive work up was negative. Her tumor burden, if any, is too minimal to account for such profound symptoms. Reintroduction of her chemo has been uneventful. The antecedent antibiotic prompts consideration of a drug reaction. Drug Reaction and Eosinophilia with Systemic Symptoms (DRESS), Serum Sickness, and Stevens-Johnson can present with fever and rash, but none develop this rapidly nor do they account for her angioedema. The patient's urticaria, angioedema and hypotension meet criteria for anaphylaxis and she responded appropriately to treatment. Anaphylaxis is an immediate hypersensitivity reaction, so the 10 hour delay in symptom onset argues against an IgE mediated process. Anaphylactoid reactions are pseudoallergies that are clinically identical to anaphylaxis except anaphylactoid reactions can have a delayed presentation following drug exposure. This pseudoallergy results from direct stimulation of mast cells without cross linking to IgE. This explains why penicillin skin testing is negative in anaphylactoid reactions and positive in anaphylaxis. In the acute setting, anaphylaxis and anaphylactoid reactions are treated identically. Unlike IgE mediated reactions, pseudoallergies do not always preclude reexposure to the offending drug. One cases series found that if a reaction to a cephalosporin occurred greater than 1 hour after exposure and the patient had negative skin testing, they completely tolerated reexposure to the drug. Neither anaphylactic nor anaphylactoid reactions result in fever or neutrophilia. However, the recurrent fever and simultaneous flares of urticaria suggest that they were linked. She did receive G-CSF which is associated with fever, neutrophilia, and a heightened neutrophil functionality. In vitro, these G-CSF primed neutrophils have been shown to release significant quantities of IL-6 when exposed to TNF-alpha. Mast cells are a significant source of TNF-alpha. Together, TNF-alpha and IL-6 produce fever. This novel clinical combination of mast cell degranulation stimulating G-CSF primed neutrophils appears to be the perfect cytokine storm for an anaphylactoid induced fever. Further study into the exact mechanism and biomarkers are warranted.
ACQUIRED ACRODERMATITIS ENTEROPATHICA: RECOGNIZING ZINC DEFICIENCY FOLLOWING GASTRIC BYPASS SURGERY
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LEARNING OBJECTIVE 1:
Describe a classic presentation of zinc deficiency

LEARNING OBJECTIVE 2:
Recognize the potential nutritional deficiencies following gastric bypass surgery

CASE:
A 54 year-old Caucasian woman with a history of Crohn's disease, Roux-en-Y gastric bypass surgery, and chronic kidney disease, presented with a progressive skin rash for several months. The patient noted a red rash with cracked and sloughing skin around her groin, buttocks, and upper extremities. The rash did not resolve with the use of topical corticosteroids or both topical and oral anti-fungal agents. She denied any fevers or new medications, but did have several weeks of associated diarrhea. She underwent a Roux-en-Y gastric bypass surgery about eight years prior and endorsed poor eating habits and compliance with her vitamin supplements. The physical exam revealed a middle-aged appearing female in no distress. She was afebrile with stable vital signs. She had an erythematous, desquamating rash associated with excoriations and honey-colored crusting. The rash was predominant over her perioral, lumbosacral and inguinal regions. Her distal extremities also displayed palmar erythema and fissuring. The remainder of her exam was unremarkable A skin biopsy revealed non-specific histologic findings of parakeratosis, impetiginized regions, and chronic inflammation with dermal edema. A work-up for infections and autoimmune etiology was non-revealing. The patient was found to be nutritionally deficient with an albumin level of 1.4 gm/dL. Further evaluation for micronutrient deficiencies revealed a markedly low plasma zinc level of 0.31 μg/ml (normal 0.55-1.50 μg/ml). She was diagnosed with acquired acrodermatitis enteropathica secondary to zinc deficiency and was started on zinc supplementation. A near-complete resolution of the rash was noted at follow-up four weeks later.

DISCUSSION:
Bariatric surgery is one of the fastest growing surgical procedures in the United States. The Roux-en-Y gastric bypass surgery, the most commonly performed type of bariatric surgery, divides the stomach into two unequally sized pouches and connects the smaller pouch to the jejunum, effectively bypassing the duodenum and part of the proximal jejunum. Although intraoperative and early postoperative complications are rare and compare favorably with other frequently performed abdominal operations, late complications are becoming more visible. Micronutrient deficiencies are the most likely long-term complication and often present as clinical syndromes classic for the deficiency. Zinc is an essential cofactor for enzymes involved in keratinocyte maturation, among several other regulatory processes. Acquired acrodermatitis enteropathica, or zinc deficiency due to impaired metabolism, classically presents as a perioral, intertriginous, and acral dermatitis that may be associated with diarrhea, alopecia, and altered mental status. The dermatitis appears as erythematous patches of dry and scaly skin, an eczematous rash, or a vesiculopustular eruption. Several mechanisms contribute to the micronutrient deficiencies seen after bariatric surgery, including decreased oral consumption, impaired intestinal uptake, poor compliance with dietary supplementation, and pre-existing nutritional deficiencies seen in obesity. Zinc levels may be low pre and postoperatively; however, when symptomatic, oral repletion rapidly corrects symptoms, as in this patient. This case also illustrates the importance of recognizing nutritional deficiencies in patients who undergo bypass surgery. Other common deficiencies include vitamin B12, folate, iron, copper, calcium, and vitamin D. There are not any randomized-controlled trials that guide general practitioners on screening and supplementation; however, awareness of such deficiencies may lead primary care physicians to reinforce dietary compliance with their patients and more easily identify the signs and symptoms of micronutrient deficiencies when they occur.