Austrian Syndrome: A Rare Triad

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Learning Objective 1: Increase awareness of a deadly clinical syndrome, rare now in a culture of pervasive antibiotic therapy

Learning Objective 2: Recognize the association of pneumonia, endocarditis and meningitis seen with invasive pneumococcal bacteremia

Case: A 64 year old male, with no medical history, presented in respiratory distress to the emergency department. The patient had not seen a doctor in twenty years and had been ill for three weeks with cough, fever and lethargy. The patient’s wife admitted the patient had a significant history of alcohol and tobacco use. On the day of admission, the patient was found lying on the floor nonverbal and disoriented. A chest x-ray found a right upper lobe infiltrate and an EKG revealed Afib with RVR. Early differential diagnosis included meningitis/encephalitis vs. CVA vs. sepsis. A lumbar puncture revealed hazy CSF, glucose <1, WBC 174 and neutrophils 86. The patient was admitted to the intensive care unit for management of VDRF, meningitis, pneumonia and rate control of Afib.

The patient was initiated on broad spectrum antibiotics and dexamethasone. Microbiology results returned positive for pneumococcal urinary antigen, as well as blood cultures positive for s. pneumonia. Given the presence of disseminated bacteremia, the patient underwent TEE which revealed a mitral valve vegetation of 0.4 cm and a 0.3cm aortic valve vegetative strand. Since there was no evidence of aortic insufficiency and only mild mitral regurgitation, valve replacement was deferred and the patient was managed medically. Numerous MRI’s were performed which revealed development of and subsequent worsening subdural empyemas. The patient deteriorated over the course of his ICU stay. Eleven days after admission, the patient suffered a cardiac arrest but was successfully resuscitated. With no clinical improvement and continued deterioration, discussions with family ultimately yielded a decision for comfort care.

Discussion: Invasive pneumococcal illness is a rare clinical occurrence, with only 54 cases having been reported. In 1881, Osler wrote, “Meningitis is a very rare complication of pneumonia and may occur apart from endocarditis…” Today, with common use of antibiotics, invasive pneumococcal disease is rare, yet still carries a high mortality. The triad, now termed Austrian syndrome, was described in a 1956 paper by Robert Austrian. Patients typically are chronically ill males in their 5th-6th decade and have a history of alcoholism. Other risk factors include splenectomy, dural fistulas and immunosuppression. Endocarditis is typically left sided and predominantly involves the aortic valve. However, there are subtle presentations which involve the mitral valve. Our case is unique in that both the aortic and mitral valves exhibited vegetations. Given increasing rates of penicillin resistance, effective treatment necessitates analyzing antibiotic sensitivities. In patients with indications for valve replacement, urgent surgery has been associated with more favorable outcomes rather than conservative management. Dexamethasone has been shown to improve outcomes in patients with pneumococcal meningitis and in patients with Austrian syndrome. Despite medical and surgical advancements since Osler first described the triad in 1881, invasive pneumococcal infection still carries a high mortality. Prompt diagnosis and aggressive treatment are tantamount to surviving this severe infection.
A Case of Multiple Myeloma Involving the Thyroid Gland

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Learning Objective 1: Recognize that multiple myeloma can present with a thyroid mass.

Learning Objective 2: Understand that biopsy of a thyroid mass is necessary in euthyroid patients with suspected malignancy.

Case: A 61-year-old white female presented with a neck mass that had enlarged over four months coupled with an unintentional ten pound weight loss. Her past medical history was pertinent for questionable monoclonal gammopathy of undetermined significance.

Her physical exam was remarkable for a large, hard, and uneven thyroid mass that moved with deglutition. Cervical lymphadenopathy was absent. Complete blood count (CBC) showed a hemoglobin of 7.6 g/dL with a platelet count of 37,000. Peripheral smear showed Rouleaux formation. The creatinine was 1.2; total protein was 7.6, and the albumin 3.7. Serum calcium was 17mg/dL. Urinalysis revealed 2+ proteinuria, but no urinary light chain was detected. Thyroid studies were normal. Serum lactate dehydrogenase was 1066IU/L. The serum immunoglobulins were as follows:

- IgA- 23mg/dL
- IgG- 2300mg/dL
- IgM- 28mg/dL

Serum protein electrophoresis (SPEP) and serum immunofixation confirmed monoclonality. The serum free light chain assay yielded IgG Kappa of 19.4mg/L and Lambda as 0.3mg/L, with a Kappa/Lambda ratio of 61 (abnormal <0.03 or >32).

Computed tomography (CT) of the neck showed a 10x8x8cm thyroid mass. Positron emission tomography (PET)/CT showed a high standardized uptake value (SUV) in the mass. Skeletal survey showed no osteolytic lesions, and magnetic resonance imaging (MRI) of the spine and pelvis showed no lytic lesions or spinal cord involvement.

Biopsy of the mass showed diffuse infiltration with multiple clonal plasma cells, and biopsy of the bone marrow exhibited 90% plasma cells with Kappa light chain, CD 138 positivity.

Discussion: Multiple myeloma (MM) is a malignant plasma cell disorder of the bone marrow. Extramedullary involvement is uncommon, and thyroid involvement is extremely rare, with only three reported cases in the global literature. Although there are many case reports of solitary plasmacytomas involving the neck or thyroid cartilage, this case represents multiple myeloma presenting in the thyroid, with CD138-positive monoclonal plasma cells. It is important to differentiate between extramedullary MM and solitary plasmacytoma because of the stark contrast in prognosis between the two.

Local radiotherapy leads to long-term clinical stability in at least 90% of cases of solitary plasmacytoma, and unless complication warrants surgical intervention, the radiotherapy is sufficient for an average 10 year survival. However, MM carries with it a worse prognosis, especially in cases with extramedullary spread, thus identification of MM early can increase survival in those afflicted. This means a high clinical suspicion for those at risk (e.g., a history of MGUS) even if the classic vertebral presentation is not suspected.

One should always consider unusual locations, such as the central nervous system, lungs, sphenoid sinus, orbit, ovaries, colon, liver/spleen, and thyroid, as potential extramedullary presentations of MM. If suspicion is high, urgent biopsy and laboratory analysis should be ordered to evaluate for MM. The difficulty arises in quantifying suspicion for those in primary care to ensure MM is caught early; we present a case that lays the foundation for establishing these guidelines.
An Unlikely Culprit Creating an Uncontrolled INR

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Learning Objective 1: Recognize that in patients on warfarin, moderate doses of acetaminophen can significantly raise the INR

Learning Objective 2: Discuss the mechanism of this drug-drug interaction, via direct effect of acetaminophen on the vitamin K cycle, not hepatotoxicity or alterations in warfarin metabolism

Case: A 63 yo man with multiple prior DVTs on long-term warfarin therapy presented with rectal bleeding. He was compliant with medications, had no changes to his warfarin dosing, no recent antibiotic or herbal supplement use, and no changes in dietary habits. He fell two weeks prior to admission and was using acetaminophen 650 mg q6h for severe wrist pain. On the day of admission, the patient was seen by his primary doctor and had an INR of 7.5 – it was 2.3 three weeks prior; he was advised to hold warfarin and go to the ED if he began to bleed. Later in the day after having a bowel movement he saw blood on the toilet paper and in his underwear but had no abdominal pain, blood in the actual stool, or change in stool color. The bleeding resolved with EMS applying pressure to the area on the way to the ED. PE revealed external hemorrhoids with evidence of recent bleeding. Labs were INR of 9.8, hemoglobin 10.4, LFTs normal. He was given vitamin K 2 mg sq in the ED and 2.5 mg PO. After admission he had no more bleeding episodes, with vital signs and CBC remaining stable. An x-ray revealed a distal radial fracture which was treated by splint immobilization and oxycodone. The INR decreased to 2.6 within 48 hours, and the patient resumed his home dose of warfarin. He was advised to stop acetaminophen, as this was a possible etiology for the elevated INR.

Discussion: Acetaminophen is generally the analgesic of choice for people on warfarin. It is considered to have a better safety profile than aspirin or NSAIDs, which predispose people to increased bleeding through platelet inhibition or injury to gastric mucosa. However there is a recognized but underappreciated drug-drug interaction which causes an elevation in INR if acetaminophen is taken at moderate doses of 1.5-4 grams per day for over 3 days. These doses are generally considered safe from a hepatotoxicity standpoint. This interaction was first reported in 1968, and several early cases described this potentiating effect of acetaminophen on warfarin. Prospective randomized trials studying this relationship have found a statistically significant rise in the INR and bleeding episodes at the previously mentioned doses. The explanation as to how acetaminophen effects the INR of patients on warfarin is quite novel. As opposed to other agents that alter the metabolism of warfarin thus increasing or decreasing its effect, acetaminophen acts through its metabolite NAPQI causing a direct inhibition of the vitamin K cycle. Vitamin K is reduced to its active form by vitamin K reductase (VKOR), the enzyme inhibited by warfarin. NAPQI disrupts the vitamin K cycle directly, including direct inhibition of VKOR and raising the INR of patients on warfarin. Currently there are no specific recommendations on reversing over-anticoagulation from the combination of warfarin and acetaminophen, outside the general recommendations of treating an elevated INR. Thus, patients on warfarin who are on significant doses of acetaminophen for several days should have the INR closely monitored for any possible interaction.
When Blood Doesn't Help

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Learning Objective 1: Recognize the signs and symptoms of Delayed Hemolytic Transfusion Reaction

Learning Objective 2: Understand the indications for transfusion and possible adverse outcomes in a patient with Sickle Cell Disease.

Case: A 30 year-old woman with a history of Sickle Cell Disease (Hemoglobin SS), complicated by monthly vasooclusive crisis (VOC), presented with acute onset chest pain. She described the pain as a "typical" VOC. On presentation she was febrile, tachycardic, tachypnic, hypoxic, and was noted to have scleral icterus and moderate respiratory distress. Laboratory studies revealed a hemoglobin (Hb) of 4.9 G/dL, (baseline Hb 7 G/dL), reticulocytes 24%, lactate dehydrogenase (LDH) 1400 U/L (600 during prior crisis), and an indirect bilirubin of 2.6 mg/dl. Chest xray was significant for a left lower lobe infiltrate. Given the presumed diagnosis of acute chest syndrome, and the significant drop in Hb from baseline, an urgent blood transfusion was ordered. Type and screen was drawn prior to transfusion and she was emergently transfused one unit of type O negative blood, with the goal to increase Hb to a safer level prior to exchange transfusion. Repeat Hb post-transfusion decreased to 4.2 G/dL and LDH increased to 1900 U/L. Subsequently, type and screen drawn prior to transfusion was noted to be positive for Anti-Jkb antibody. After review of the electronic medical record it was noted that the patient was seen in the ED two weeks prior to the current admission for VOC and was transfused 2U PRBCs. Type and screen prior to transfusion at that time was negative for autoantibodies. A diagnosis of Delayed Hemolytic Transfusion Reaction was made. The patient was started on high dose methylprednisolone, epoetin and iron infusion. Hb trended upward to 6.5 g/dL without receiving further blood products, with complete resolution of her presenting symptoms.

Discussion: Sickle cell disease is a common disorder seen by general internists. These patients often receive blood transfusions during inpatient hospitalizations, although they are not always evidence based. It is critical to understand the risks and benefits of transfusion; including the indications for transfusion. We report a case of delayed hemolytic transfusion reaction (DHTR). Indications for transfusion in a patient with sickle cell disease include acute stroke, acute chest syndrome, acute multi-organ failure, acute symptomatic anemia, and reticulopenia (e.g. parvo-B19 induced). The adverse risks of transfusion include febrile non-hemolytic reaction, acute hemolytic reaction, anaphylaxis, transfusion associated acute lung injury, and DHTR. The incidence of DHTR occurs in 1:5000-10,000 units packed red blood cells transfused; often 3-21 days post transfusion. DHTR is clinically characterized by hemolysis, fever, a positive antiglobulin on Coombs test, and a new positive antibody screen. DHTR is a primary immune response where the recipient generates non-complement binding antibodies that coat donor red blood cells (RBC) leading to extravascular hemolysis. DHTRs are often mild and do not require treatment. On rare occasions hyperhemolysis may occur, requiring symptomatic management. It is important to consider the diagnosis of DHTR as further transfusions often worsen DHTRs or lead to a hyperhemolysis syndrome due to re-exposure to foreign RBC antigens. Treatment is often supportive with steroids to ameliorate immune response and erythropoietin with iron transfusion in an effort to increase hemoglobin production.
A Puzzling Case of Nausea Ad Nauseam

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Learning Objective 1: Recognize causes of thyroid dysfunction in the context of primary adrenal insufficiency.

Learning Objective 2: Consider adrenal insufficiency in a symptomatic hypothyroid patient who worsens with thyroxine replacement.

Case: A 58-year-old woman presented with 10 days of worsening nausea, vomiting, fatigue, generalized weakness and dry cough. Her medical history was significant for hypothyroidism diagnosed 18 months ago when she presented to her primary care provider for unremitting nausea. Work up at that time revealed a TSH 7.4 mIU/L, normal T3, T4, TPO antibodies and she was started on thyroxine replacement, though her symptoms worsened.

On presentation to our institution, her blood pressure was 61/50 and pulse was 60. Physical examination revealed decreased skin turgor, dry mucous membranes and hyperpigmentation of her face, neck, arms and palmar creases. Over the last year, she noted compliments on her “tan” and questions regarding “dye” on her palms. Labs showed a normocytic anemia (hemoglobin, 9.9 g/dL), hyponatremia (124 mmol/L), hyperkalemia (6.0 mmol/L) and raised creatinine (1.2 mg/dL). Chest x-ray suggested an atypical pneumonia and a random cortisol returned low at 4.2 mcg/dL. She received 9 liters of IV fluids, antibiotics, and stress doses of dexamethasone were initiated due to concern for adrenal crisis. She had rapid clinical improvement with resolution of her nausea. Adrenal function tests confirmed primary adrenal insufficiency with baseline AM cortisol < 1.0 mcg/dL, which minimally increased to 1.3 mcg/dL 30 minutes after cosyntropin challenge (0.25mg IV), and aldosterone < 4.0 ng/dL. Repeat TSH was 2.4 mIU/L while on thyroxine. Abdominal CT and extensive infectious workup was unremarkable, while a 21-hydroxylase antibody level was elevated (60 U/mL), confirming the diagnosis of autoimmune adrenalitis.

Discussion: We describe a case of unrecognized primary adrenal insufficiency in which elevated TSH along with symptoms suggestive of adrenal insufficiency may have been a first clue to early diagnosis. Thyroid function abnormalities are often seen with adrenal insufficiency given that cortisol deficiency impairs thyroid function resulting in an elevated TSH. During crises, thyroxine replacement can accelerate cortisol degradation exacerbating symptoms of hypocortisolism, and should be avoided. In the absence of autoimmune thyroid disease, thyroid function abnormalities often resolve with glucocorticoid replacement.

Alternative thyroid dysfunction may be secondary to coexisting autoimmune hypothyroidism, supported by elevated antibodies to thyroglobulin or anti-thyroid peroxidase, suggesting autoimmune polyglandular syndrome (APS1 or APS2). APS2 is inheritable, more prevalent and characterized by autoimmune thyroiditis, autoimmune adrenal insufficiency and type 1 diabetes mellitus.

18 months prior, our patient had negative TPO antibodies, thus coexisting autoimmune hypothyroidism (and APS) was thought to be less likely. Because her symptoms worsened with thyroxine replacement, it is likely that her elevated TSH was due to adrenal insufficiency. The patient was discharged with endocrinology follow up for optimizing steroid doses and discontinuation of thyroxine.

This case highlights the importance of maintaining a wide differential when working up chronic nausea and fatigue, especially in the setting of thyroid abnormalities. Adrenal crisis is potentially life threatening, and early diagnosis of adrenal insufficiency may help prevent an acute decompensation.