Review Article: Care of the Hospitalized Patient with Cystic Fibrosis: A Summary of Current Practice Guidelines; Recommendations for the Hospitalist, Part 1 (Pulmonary Exacerbation)

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In the past, it was rare to see patients with cystic fibrosis (CF) on adult inpatient services as patients' lifespans were limited. In 1955, most children with CF were not expected to live long enough to attend elementary school. Today the predicted median survival is in the early 40's. This is largely due to the care provided through the national network of CF Foundation-accredited centers. This is a nationwide network of more than 110 centers where teams of experts in the care and management of CF treat people living with this disease. The CF Foundation's Care Center Network has been cited by the National Institutes of Health as a model of effective and efficient health care delivery for a chronic disease. Each center undergoes regular review of practices by the Foundation Center Committee prior to accreditation and funding. The national registry of the Cystic Fibrosis Foundation (cff.org), a registry that collects information from more than 27,000 people with CF who have agreed to share their medical data for research purposes, expects that the total number of adult patients will soon exceed the total number of patients younger than 18. Most CF patients receive care from CF specialty centers. CF specialty centers work in collaboration with local medical providers to deliver coordinated care for these complicated patients.

While pediatric providers have historically cared for this population's needs throughout their shortened lives, CF patients now rarely succumb to this disease in childhood and increasingly seek care from adult providers. We now expect to see CF patients for decades after they turn 18. It is for this reason adult Hospitalists should become proficient in recognizing the needs and providing for the management of the hospitalized CF patient. The existing literature puts forth well-reviewed and extensively studied clinical practice guidelines for the care of a hospitalized patient with symptoms of a Cystic Fibrosis pulmonary exacerbation. These are consensus reports based on the accumulation of evidence in Cochrane reviews as well as the cumulative experience of a number of experts representing the larger CF care community. The purpose of this series of articles is to summarize this body of work for the generalist and point out the resources available to the providers at the bedside. It will initially cover the basics of an admission, and in subsequent installments will expand the discussion of care to include the complications

Hospitalists see in caring for these patients. Below is an outline of the basic evaluation and management of a patient presenting with a pulmonary exacerbation:

1. Recognition of need for hospitalization
   a. Symptoms-pulmonary (GI symptoms predominate when patient presents with DIOS*)
      i. Hemoptysis
      ii. Cough
      iii. Changes in the character of the sputum
      iv. Chest pain
      v. Anorexia/vomiting
   b. Signs
      i. Increased work of breathing
      ii. Fever
      iii. Weight loss
      iv. Changes on pulmonary exam (abdominal exam)
   c. Data
      i. Hypoxemia
      ii. Decline in lung volumes as measured by pulmonary function testing (PFT) or spirometry
      iii. Change in CXR or other imaging
      iv. Leukocytosis
      v. Change in microbial inhabitants of the sputum
2. Rationale of treatment
   a. Based on pathophysiology of the disease (abnormal mucus)
   b. Guided by microbiology of airway
      i. Chronic colonizers
      ii. Viral infections
      iii. Mycobacterium
      iv. ABPA (allergic/inflammatory response to aspergillosis)
   c. Measured by;
      i. Symptom resolution
      ii. Recovery of lung volumes
3. Setting
   a. Home
   b. Hospital (specific floor)

- Special considerations

   a. IV access
   b. Infection control (private room and shower, rounding on patients)
   c. Exercise (DVT prophylaxis and another form of chest physiotherapy)

d. Access to calories (extra food, enzyme replacement)
　　　　　e. IV fluids
　　　　　f. Pregnancy testing

1. Therapies
　　　a. Oxygen
　　　b. Antibiotics
　　　c. Airway clearance therapies
　　　d. Nutrition
　　　e. Bowel program
2. Complications
　　　　　a. Hemoptysis

3. Pneumothorax
4.
　　　a. Pain
　　　b. Hepatic, renal and neurologic disturbances
　　　c. Nausea, vomiting, diarrhea, and/or steatorrhea
　　　d. CF-related diabetes
　　　e. Rectal prolapse
　　　f. Urinary incontinence
5. Monitoring/surveillance
　　　a. Weights
　　　b. Pulse oximetry
　　　c. Labs
　　　d. Culture data
　　　e. Blood sugars
　　　f. Imaging
　　　g. Immunizations and preventive care
6. Collaboration/consultation
　　　a. CF team, (CF doctor, CF dietician, CF nurse, CF respiratory therapist, CF social work, CF psychologist, pulmonologist and intensive care specialists)
　　　b. GI, ENT, Endocrinology
7. Transplant
8. End-of-life care

*Patients with cystic fibrosis can present for acute care for other reasons unrelated to lung disease, including; the development of DIOS, pancreatitis in the pancreatic-sufficient patient, pregnancy management, infertility workup and treatment, complications of cirrhosis as a result of CF-liver disease, and complications of CF-related diabetes.

PATHOPHYSIOLOGY

For an detailed discussion about the pathophysiology of cystic fibrosis, I will refer to the resource information. In brief, cystic fibrosis is a complex genetic disease affecting many organs, although 80-90% of the mortality is a result of lung disease. Cystic fibrosis lung disease begins early in life and is a result of mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) protein. CFTR functions as a chloride channel in epithelial membranes. Insufficiency of the protein leads to pathologic changes in organs that express CFTR. These include secretory epithelial cells of many organs including; sinuses, lungs, pancreas, liver, the reproductive tract and sweat glands in the skin. The most striking change occurs in the airway surface liquid. Electrolyte changes in the airway lead to the following complex interactions:

1. Abnormal mucus resulting from dehydration of the airway surface liquid layer
2. Impaired mucociliary clearance
3. Colonization of the airway with multiple organisms **
4. An exaggerated, sustained, and extensive inflammatory response to the pathogens in the airway

** Pseudomonas aeruginosa (Ps a.) has long been recognized as a significant pathogen in disease progression. Other recognized agents include methicillin-resistant Staphylococcus aureus (MRSA), Achromobacter species, Stenotrophomonas maltophilia, Burkholderia cepacia and non-tuberculosis mycobacteria (NTM). Studies have shown that these strains lead to worsening symptoms and can speed the decline in lung function.

PULMONARY EXACERBATION

Recognizing the need for treatment is the first step in management of a pulmonary exacerbation. Most patients with cystic fibrosis can recognize a change in symptoms and will either present to the outpatient clinic with new complaints (increased cough, increased amount of sputum with thickening and difficulty in airway clearance, chest pain, dyspnea, fatigue, new oxygen need, etc.) or contact the Cystic Fibrosis Center to report changes from baseline. Physical examination and pulmonary function testing will often confirm an exacerbation of lung disease. Patients can be treated with an outpatient course of antibiotics if symptoms are not too severe; however, with more significant symptoms such as hemoptysis, weight loss, fevers, hypoxemia or failure to recover after a course of oral antibiotics, patients will require hospitalization. Treatment of a pulmonary exacerbation is largely based on three elements: antimicrobial treatment, aggressive airway clearance, and adequate nutrition.

ANTIMICROBIAL TREATMENT

As previously mentioned, treatment therapies are based on the pathophysiology of the disease and the presence of abnormal mucus in the airway. The microbiology of the airway also guides the choice of therapies. The airway in CF is often chronically colonized by more than one bacterial agent and is also susceptible to periodic infection by viral agents as well as Mycobacterial species. In addition, the CF airway can demonstrate the allergic/inflammatory response of ABPA (allergic bronchopulmonary aspergillosis). For this reason, sputum is generally collected at every clinic visit and at the onset of a hospitalization for culture and sensitivities. Generally, AFB is checked approximately every 6-12 months and total IgE is

monitored yearly. If the patient is unable to expectorate a sample for culture, bronchoscopy should be considered. Choice of initial antibiotic therapy is based on the identity and sensitivities of the organisms known to be present in the airway until new culture data can be obtained. In addition, most CF care providers double cover Pseudomonas (use two different active agents against the bacterium). Trials with single antibiotics have not shown equal efficacy. There is insufficient evidence to recommend for the simultaneous use of inhaled and IV antibiotics; however it is frequently practiced. There are currently no studies which define the optimal duration of antibiotics for a pulmonary exacerbation of cystic fibrosis. The practice is generally to let symptoms and lung volume measurements guide duration of therapy.

Patients with Ps a. and strains of NTM are frequently on chronic oral antibiotic treatment. In general, these agents should not be discontinued during a hospitalization but continued along with appropriate IV antibiotics. CF care center physicians should provide assistance with choice of antimicrobial agents. Pharmacists at CF centers also play a crucial role in the care of these patients. At our center we ask for pharmacy dosing assistance to achieve appropriate dosing of aminoglycosides and vancomycin.

Access for IV antibiotics may require the placement of a PICC line in those without an existing port. Patients with cystic fibrosis should be housed on a hospital floor where staff members are experienced in the care of these patients. This includes attention to infection control procedures, private rooms and showers, opportunities for exercise, consistent care of PICC lines and ports, access to supplemental nutrition, a knowledgeable team of respiratory therapists, and a supportive environment of staff familiar with this chronic illness.

Recently, new infection and control guidelines have been drafted by the Cystic Fibrosis Foundation. The latest medical data show that the risk of spreading destructive bacteria among people with CF is greater than was previously believed. New findings include evidence that strains of different bacteria, such as Pseudomonas aeruginosa, MRSA, and NTM, have been spread between people with CF. Research also suggests that the risk of some germs spreading through the air is greater than was previously known. For these reasons it is now standard of practice to gown and glove when entering a patient's room to examine the patient or provide care. Masks are used when the patient has infections spread by respiratory droplets (i.e. influenza). This is especially important when traveling between multiple CF patients' rooms.

On June 20th, 2014 the Cystic Fibrosis Foundation announced that updated guidelines for infection prevention and control have been endorsed by the Society for Healthcare Epidemiology of America (SHEA) and the Association for Professionals in Infection Control and Epidemiology (APIC). The updated guidelines will be published online in Infection Control & Hospital Epidemiology, the official journal of SHEA, within the next several weeks.

AIRWAY CLEARANCE THERAPY

Along with systemic antibiotics, airway clearance or pulmonary toilet is critical to the recovery of the CF patient. This includes a "package" of treatments referred to as airway clearance therapy (ACT). The treatment consists of specific aerosolized medications combined with mechanical airway clearance. This treatment package has been specifically intended for the abnormal airway

of a cystic fibrosis patient with impaired mucociliary clearance. (A component of reactive airways disease often exits as well). ACT begins with a bronchodilator, such as albuterol, followed by either a mucolytic or a mucous hydrator, Pulmozyme, and hypertonic saline (7% saline). During these inhaled treatments, patients use chest physiotherapies such as external high-frequency chest compression ("the vest") or airway oscillating techniques such as flutter, Acapella, Coronet, EZpap or IPPV. This mechanical clearance is cycled and interspersed with intermittent "huff-cough." The purpose of these techniques is to stimulate clearance of mucus from the airway. These therapies are "stepped up" or intensified during the hospital stay with a goal of 4-5 treatments per day (the well CF patient may only do 2 treatments per day). A combination of ACT modalities is often used. Hospitalization may provide an opportunity for patients to be introduced to new forms of airway clearance therapy. The respiratory therapy department or hospital practice must also provide equipment cleaning or replacement of tubing, handsets and other "contaminated" equipment regularly to prevent further contamination and spread of infection. CF teams have respiratory therapists well-versed in ACT and management of equipment. A review of home and hospital ACT equipment maintenance and cleaning procedures should be performed with patients regularly. To assist in infection control, it is best that patients bring their own vest with them to each hospitalization to ensure proper fit. This also decreases the risk of transmission of infectious agents between patients who share equipment. It is only after airway clearance has been effectively completed that it is appropriate to deliver inhaled antibiotics to the airway.

NUTRITION

The CF Foundation has been collecting data from the accredited CF Centers for many years. There is strong evidence that lung health is best maintained by achieving and maintaining adequate nutrition in CF patients. Target BMI values have been determined for adult male and female patients in addition to children. Weight loss is directly associated with a decline in pulmonary function. Caloric needs far exceed that of a healthy young person (2-3 times), even during wellness. Caloric needs are even greater during illness. Extra calories compensate for malabsorption and meet the greater energy needs in pulmonary disease. Pancreatic enzymes are critical for those patients who have pancreatic insufficiency. Fat-soluble vitamin supplements (vitamins A, D, E, and K) are also needed due to poor absorption. Vitamin K may be deficient in those with hemoptysis and is used routinely in massive hemoptysis even before lab values confirm a deficiency. CF teams always have a dietician trained in the management of CF malnutrition.

IMAGING:

A two view chest x-ray does not consistently demonstrate detectable infiltrates. It is often not informative of a pulmonary exacerbation. This is due to several reasons, including:

1. The extent of disease and resultant damage to the anatomy with extensive scar in the lungs which may obscure infiltrates.
2. A chest film seems to have less "sensitivity" to a pulmonary exacerbation than lung volumes and patient-reported symptoms.

3. The chronicity of bacterial colonization, which is often not localized to a particular part of the lung but is scattered throughout the anatomy. There may be many "small pneumonias."
4. CF disease is in the airway (bronchi, bronchiole) and the alveoli are the "innocent bystanders" of inflamed tissues of the airway.

(For billing purposes, it is our practice to refer to pulmonary exacerbations as "broncho-pneumonia" along with the terminology "pulmonary exacerbation of cystic fibrosis" to aid billing and coding personnel).

Other imaging performed for CF patients include: a yearly abdominal ultrasound as a screen for hepatic and renal disease, periodic bone scans due to poor absorption of vitamin D and malnutrition associated with this disease, and CT scans of sinus and lungs.

LABORATORY STUDIES:

*General chemistry to include renal and liver panels

*Complete blood count to evaluate for leukocytosis or anemia

*Sputum culture labelled with "Cystic Fibrosis" and yearly AFB

*Pregnancy testing in females

* Testing for influenza may be indicated

*To meet guidelines, patients may need additional testing such as vitamin levels, PT/INR, total IgE, Hgb A1C, GGTP

Our next discussion article on CF will quiz the reader over the preceding information and point out "pearls" to remember.

RESOURCES

1. Cystic Fibrosis Adult Care: Consensus Conference Report. Yankaskas J, Marshall B, Sufian B, Simon R, Rodman D; Chest 2004;125;1-39 http://chestjournal.org
2. Cystic Fibrosis Foundation http://cff.org
3. Cystic fibrosis foundation-Care Center reporting; http://www.cff.org/CCNP/DataPurposeUsage/
4. Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health; Flume et al; American Journal of Respiratory And Critical Care Medicine 2007;176:957-969
5. Cystic Fibrosis Pulmonary Guidelines: Treatment of Pulmonary Exacerbations; Flume et al; American Journal of Respiratory and Critical Care Medicine 2009; 180:802-808

Review Article: Determining the Optimal Steroid Treatment Regimen for COPD Exacerbations: A Review of the Literature

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Background

The literature has established that the use of systemic corticosteroids in COPD exacerbations decreased time to recovery, decreased hypoxemia, and improved FEV1.[1,2,3,4] However, the dose and duration of corticosteroids used to treat COPD exacerbations is highly variable and has been widely debated. Previous Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend 30-40mg of oral prednisolone daily for 10-14 days.[5] The most recent iteration of the guidelines recommended considering even shorter durations of 5 days based on the findings from the recently published REDUCE trial.[6,7] Due to side effects of steroids such as blood glucose elevations, emotional lability, and predisposition to fractures, especially at cumulative doses >1g prednisone or the equivalent,[8,9] it is important to limit exposure if possible. This review offers some considerations when treating COPD exacerbations in a variety of patient populations.

Treatment considerations

IV vs. PO
One of the founding studies demonstrating the clear role of glucocorticoids in the management of COPD exacerbations was published in 1999 by Niewoehner and colleagues.3 This study comparing placebo versus 2 and 8 weeks of steroid therapy found that prolonged steroid use did not have an advantage over 2 weeks of therapy. Because of this, many clinicians adopted this 2 week treatment regimen of IV methylprednisolone on days 1-3 at 125mg every 6 hours followed by 60mg of prednisone tapered by 20mg every 4 days3 as their standard of care. While this regimen did demonstrate a clear benefit, further studies have shown that high-dose IV steroids are likely not required in the management of acute exacerbations in most patients.10,11

Clinician adoption of high-dose IV steroid administration was demonstrated in a pharmacoepidemiological cohort study that looked at 79,985 patients admitted for COPD exacerbations. Investigators found that despite recommendations to utilize low-dose oral therapy for the initial management of exacerbations, 92% of patients were started on high-dose IV steroids. The authors also found that initiating patients on low-dose oral steroids did not increase risk of treatment failure and that patients had lower median hospitalization costs.10 Another study evaluating 60mg of IV methylprednisolone compared to 60mg of oral prednisolone for 5 days, followed by 30mg of prednisolone tapered over 6 days in both treatment arms, also supported the claim that oral steroids are non-inferior to IV steroids with regard to treatment failure.11

In addition to clinical equivalence, oral prednisone has a favorable pharmacokinetic profile with a bioavailability between 50-90% and peak serum levels occurring within 2 hours of ingestion.12 Because oral therapy has been shown to be equivalent to IV therapy, is less expensive, and decreases the risk of line-infections/complications,10 low-dose oral corticosteroids should be utilized for treating most patients' COPD exacerbations. However, certain patients may benefit from IV corticosteroid therapy and these special considerations are discussed below.

Duration

In the recently published prospective, randomized, non-inferiority REDUCE trial, 5 days of steroid treatment was found to be equivalent to 14 days of therapy with regards to 6 month re-exacerbation rates for patients presenting to the hospital with a COPD exacerbation. In this study, patients received an initial IV dose of methylprednisolone at 40mg, followed by prednisone 40mg daily. The majority of patients were classified as GOLD grades 3-4, demonstrating that shorter courses of systemic corticosteroids can be beneficial, even in patients with more severe COPD. New infections and new or worsening hyperglycemia and hypertension were similar in both treatment arms, but the cumulative steroid dose was only 379mg in the short-term treatment arm compared with 793mg in the conventional arm.6 Unfortunately, the level of care required on admission and the patients' history of exacerbations in the previous year were not noted in the patients' baseline characteristics.6 Since past exacerbations are the best predictor of future exacerbations,13 the GOLD guidelines denotes patients who have had two or more exacerbations in the past year to be at "high risk" for further exacerbations.5 This information would have been helpful in determining if 5 days of therapy is still optimal for these "high-risk" patients.

The use of short steroid tapers (e.g. less than 14 days) versus burst therapy has not been specifically addressed in the literature.14 Because of this, it is difficult to determine which (if any) patients would benefit from these therapies. Potential candidates for steroid tapers may include patients who fail burst therapy, have frequent exacerbations of 2 or more per year, and patients on chronic steroids.

Special considerations

COPD exacerbation, steroids, corticosteroids The aforementioned treatment considerations do not generally apply to COPD exacerbations requiring admission to the ICU. In many of the previously mentioned studies, this subset of patients were either excluded from analysis or the level of care was not addressed in the baseline characteristics.6,10,11,15 Two major studies specifically evaluating the efficacy of steroids in COPD exacerbations requiring ICU admission have been recently conducted. In a placebo-controlled, double-blind trial comparing placebo to IV methylprednisolone (0.5mg/kg every 6 hours days 1-3; 0.5mg/kg every 12 hours days 4-6; 0.5mg/kg daily days 7-10) in 83 ICU patients requiring mechanical ventilator support, Alia and colleagues found that patients receiving steroids required a shorter time on mechanical ventilation (median of 3 versus 4 days; p=0.04). The duration of mechanical ventilation was a composite outcome combining both conventional mechanical ventilation and non-invasive mechanical ventilation (NIMV) with the difference being driven largely by the NIMV subgroup. Additionally, investigators found that there was a decreased incidence of NIMV failure in the steroid treatment arm (0% versus 37%; p=0.004).16 Conversely, in their open-label, prospective, randomized controlled trial involving 217 mechanically ventilated patients admitted to the ICU for COPD exacerbation, Abroug and colleagues found no difference in duration of ventilation (median of 6 versus 6 days; p=0.87) or NIMV failure (15.7% versus 12.7%; p=0.59) for patients who received oral prednisone at 1mg/kg daily until discharge or up to a 10 day maximum when compared to usual care. Usual care was defined as receiving ventilator assistance, nebulized ipratropium and beta-2 agonists, and antibiotics if clinically indicated.15 While this study was underpowered to detect a difference in these outcomes, it may offer some insight into more optimal treatment regimens for patients requiring ICU admission. Patients in the Alia study received twice the amount of steroids for the first few days of admission compared to the Abroug study and this high-dose of IV steroids may have contributed to the difference seen in duration of mechanical ventilation.15

Because there is limited information regarding optimal treatment in this subgroup of patients, the dosing recommendations found in the Alia and colleagues study may be the best evidence-based treatment regimen for this patient population, especially during the first few days of treatment. Given the fact that IV steroid treatment is equivalent to oral therapy in non-ICU patients, it would be reasonable to transition to an appropriate dose of oral steroids once patients begin to clinically improve.

Summary

In reviewing the literature, there is not a uniform approach to corticosteroid treatment when managing patients with COPD exacerbations. In general it is important to remember:

- Oral corticosteroids are as effective as IV corticosteroids in the management of most COPD exacerbations not requiring ICU admission.
- Short courses of prednisone (40mg daily for 5 days) are appropriate for most COPD exacerbations.
- Patients with frequent exacerbations of 2 or more per year or patients on chronic steroids may require a prolonged course of treatment.
- ICU patients have largely been excluded or not specifically studied in most analyses. Available literature shows that this subset of patients may benefit most from high-dose IV therapy for the first few days of treatment. Once patients are clinically improving, it would be reasonable to deescalate to oral therapy to limit unnecessary exposure.

References

1. Davies L, Angus RM, Calverley PM. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomized controlled trial. Lancet. 1999; 354: 456-60.
2. Maltais F, Ostinelli J, Bourbeau J, et al. Comparison of nebulized budesonide and oral prednisolone with placebo in the treatment of acute exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. Am J Respir Crit Care Med. 2002; 165: 697-703.
3. Niewoehner DE, Erbland ML, Deupree RH, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. N Engl J Med. 1999; 340(25): 1941-7.
4. Thompson WH, Nielson CP, Carvalho P, et al. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. Am J Respir Crit Care Med. 1996; 154: 407-12.
5. Global initiative for chronic obstructive lung disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013_Feb20.pdf. Updated February 20, 2013. Accessed July 16, 2013.
6. Leuppi JD, Schuetz P, Bingisser R, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease. JAMA. 2013; 309(21): 2223-2231.
7. Global initiative for chronic obstructive lung disease: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. http://www.goldcopd.org/uploads/users/files/GOLD_Report_2014_Jan23.pdf. Updated January 23, 2014. Accessed June 6, 2014.
8. de Vries F, Bracke M, Leufkens HGM, et al. Fracture risk with intermittent high-dose oral glucocorticoid therapy. Arthritis and Rheumatism. 2007; 56(1): 208-214.
9. Walters JAE, Wang W, Morley C, at al. Different durations of corticosteroid therapy for exacerbations of chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2011; 10: 1-50.

10. Lindenauer PK, Pekow PS, Lahti MC, et al. Association of corticosteroid dose and route of administration with risk of treatment failure in acute exacerbation of chronic obstructive pulmonary disease. JAMA. 2010; 303(23): 2359-2367.
11. de Jong YP, Uil SM, Grotjohan HP, et al. Oral or IV Prednisolone in the treatment of COPD exacerbations: a randomized, controlled, double-blind study. CHEST. 2007; 132(6): 1741-1747.
12. Lexi-Comp OnlineTM [Internet database]. Hudson, Ohio: Lexi-Comp, Inc. Updated periodically. Accessed June 9, 2014.
13. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010; 363(12): 1128-1138.
14. LaBrin J, Cunningham KE. What corticosteroid is most appropriate for treating acute exacerbations of COPD?. The Hospitalist 2011. http://www.the-hospitalist.org/details/article/1072143/What_Corticosteroid_is_Most_Appropriate_for_treating_Acute_Exacerbations_of_CoPD.html.
15. Abroug F, Ouanes-Besbes L, Fkih-Hassen M, et al. Prednisone in COPD exacerbation requiring ventilatory support: an open-label randomised evaluation. Eur Respir J. 2014; 43: 717-714.
16. Alia I, de la Cal MA, Esteban A, et al. Efficacy of corticosteroid therapy in patients with an acute exacerbation of chronic obstructive pulmonary disease receiving ventilator support. Arch Intern Med. 2011; 171(21): 1939-1946.

Case Report: Transient Gestation-associated Diabetes Insipidus (GDI)

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Introduction

Diabetes insipidus (DI) is a disorder characterized by polydipsia, polyuria, and the formation of hypotonic urine. DI can be broadly classified into central DI and nephrogenic DI. In summary, central DI is due to the defective synthesis or release of arginine-vasopressin (AVP) or anti-diuretic hormone (ADH) from the hypothalamo-pituitary axis. Nephrogenic DI is due to renal insensitivity to AVP. Transient pregnancy-associated or gestational-associated diabetes insipidus (GDI) is a rare condition that occurs during the third trimester affecting between 2 and 6 cases per 100,000 pregnancies ((1, 2, 3, 4). It is thought to occur due to elevated levels of the enzyme vasopressinase, which is released from the placenta and causes the degradation of ADH (5).

During normal pregnancy the set point of the osmoregulatory system is reduced. The thirst threshold as well as the threshold for vasopressin release is also decreased. This leads to pregnant women feeling thirsty at a lower serum sodium and osmolality. The plasma sodium concentration typically decreases approximately 5meq/L early in pregnancy due to resetting of the osmoreceptors for ADH release, increased thirst, and circulatory volume dilution effects. This effect appears to be mediated by the increase in human chorionic gonadotropin. Another change is that the metabolic clearance rate of ADH markedly increases between gestational week 10 and mid-pregnancy due to vasopressinase. The activity of vasopressinase in normal pregnancy has been hypothesized to retain the fluid necessary for normal pregnancy by increasing ADH clearance and to block uterine contractions by increasing oxytocin clearance. The plasma ADH concentration usually remains normal in pregnancy as the body compensates for the increased ADH clearance. However, some women develop transient central DI as a result of excessive vasopressinase where the pituitary is unable to maintain the necessary serum ADH level. In addition, some women may have normally reduced secretory reserve of ADH. In such cases, even small increases in serum vasopressinase during pregnancy could lead to gestational associated DI. Other studies have shown transient pregnancy-associated vasopressin-resistance that does not respond to either large doses of natural ADH or Desmopressin Aceteate (DDAVP) (6).

Case

A 15 year old primigravida, with no prenatal care, presented at 32 2/7 weeks of gestation with preterm contractions, abdominal pain and an increased BP of 154/100 mmHg. She also admitted to having intermittent low back pain, nausea and vomiting for the past week. She denied bleeding, discharge or leakage of fluid per vagina. She denied any known drug allergy and was not taking any medications. She had no significant medical or surgical history and denied any social or family history. She did not have any pertinent physical findings and was not in active labor. She was placed on electronic fetal monitoring and was found to have a normal, reactive tracing with occasional contractions.

While in the hospital, prenatal labs were performed which were negative for Group B Streptococcus, negative for Gonorrhea, negative for Chlamydia, negative for Human Immunodeficiency Virus, negative for Hepatitis B Virus (also never been vaccinated), non-reactive for syphilis and Rubella immune. Initial laboratory findings showed elevated serum sodium of 153mEq/L and it was initially believed to be the result of dehydration. After

intravenous rehydration with normal saline, the serum sodium continued to rise and was 160mEq/L within 24 hours.

In addition, due to the elevated BP we also evaluated her for pregnancy induced hypertension (PIH) and ordered standard PIH labs. Urinalysis was negative for urine glucose, protein, bilirubin, ketones, hemoglobin, nitrites, and leukocytes, and had trace bacteria. Her blood counts were as follows: hemoglobin/hematocrit of 11.6/36.1, white blood cells 10.58, and platelets 307. Complete metabolic panel showed potassium 3.4, chloride 117, CO_2 31, glucose 73, BUN 6, creatinine 0.96, calcium 8.7, total protein 6.4, albumin 3.2, total bilirubin 0.3, alkaline phosphatase 358, alanine aminotransferase 18, aspartate aminotransferase 26, uric acid 6.5, lactate dehydrogenase 243, triglycerides 87, cholesterol 203 and thyroid stimulating hormone 1.180. Ultrasound and amniotic fluid index were normal. Fetal fibronectin was negative. DI was suspected and a work up was initiated. In addition, serum osmolality was also elevated. But urine osmolality was decreased. See Figures 1A – 1C. These laboratory findings strongly suggested DI associated with elevated vasopressinase.

The DI work up to differentiate between central and nephrogenic DI was initiated with monitoring of serum and urine electrolytes and osmolality. The water deprivation test was not performed, due to concerns for the wellbeing and safety of the mother and fetus. Baseline serum sodium was 160mEq/L, serum osmolality was 326mOsm/kg, urine sodium was 27.0meq/L, and urine osmolality was 84mOsm/kg prior to a DDAVP challenge. Evaluation for central vs nephrogenic DI was performed by giving the patient DDAVP 2 mcg intramuscularly (IM) followed by checking serum and urine osmolality 2 hours later. Serum sodium of 150mEq/L and urine osmolality of 180mOsm/kg was seen 2 hours after the DDAVP challenge. Since the urine osmolality had more than doubled, a central DI was strongly suspected.

DDAVP was held and the patient was instructed to take in oral free water to evaluate the patient's ability to maintain normal serum sodium and osmolality and urine sodium and osmolality for 12 hours. Unfortunately, even with the patient drinking up to 3 L of free water in 24 hours, she was not able to maintain normal electrolytes and osmolality. Her serum sodium and osmolality returned to abnormally high values and her urine sodium and osmolality returned to abnormally low levels. In fact, her urine osmolality was 39mOsm/kg. DDAVP treatment was immediately restarted at 2 mcg IM every 12 hours. The serum and urine electrolytes and osmolality were followed at 2 hours post DDAVP injection and at every 6 hours. Over the subsequent 24 hours, the patient's serum and urine electrolytes and osmolality normalized. The dose of DDAVP was decreased to 1 mcg IM every 12 hours to prevent over correction. The 1 mcg DDAVP dose appeared to be as effective as the 2 mcg DDAVP dose. Serum ADH level was also evaluated and was shown to be below detectable levels, which further supported a GDI as opposed to nephrogenic DI. See Figures 1A – 1C. Magnetic resonance imaging (MRI) of the brain did not show any pituitary mass. The fact that this patient presented in the third trimester and did not have any history of trauma or neurosurgery further supported a vasopressinase associated DI as opposed to a decreased secretory reserve of ADH or unmasking of a subclinical or overt DI due to the pregnant state. In these latter conditions, women usually present earlier in their pregnancies, when vasopressinase levels have not yet increased. We were unable to locate a laboratory that evaluated quantitative serum vasopressinase. However, we remain suspicious that this was central DI associated with excessive serum vasopressinase secretion by the placenta.

The patient follow up was arranged at the high-risk obstetric clinic with bi-weekly basic metabolic panels until delivery and likely several weeks after the delivery to ensure that the central DI has resolved. As per patients primary care provider patient delivered healthy baby afterwards with resolution of DI. This further supports a vasopressinase-associated central DI.

Conclusion

This case demonstrated that there may be women with gestational DI that go undetected, especially if they have no prenatal care. Although the full impact of undiagnosed pregnancy-associated DI is unclear, it is believed to cause an increase in morbidity and mortality for both the mother and fetus. In our review of the literature, we found that GDI presents in many different ways and it is difficult to diagnose based on symptoms alone. If a patient presents with elevated BP and a work up for preeclampsia reveals elevated serum sodium, a diagnosis of DI should be suspected.
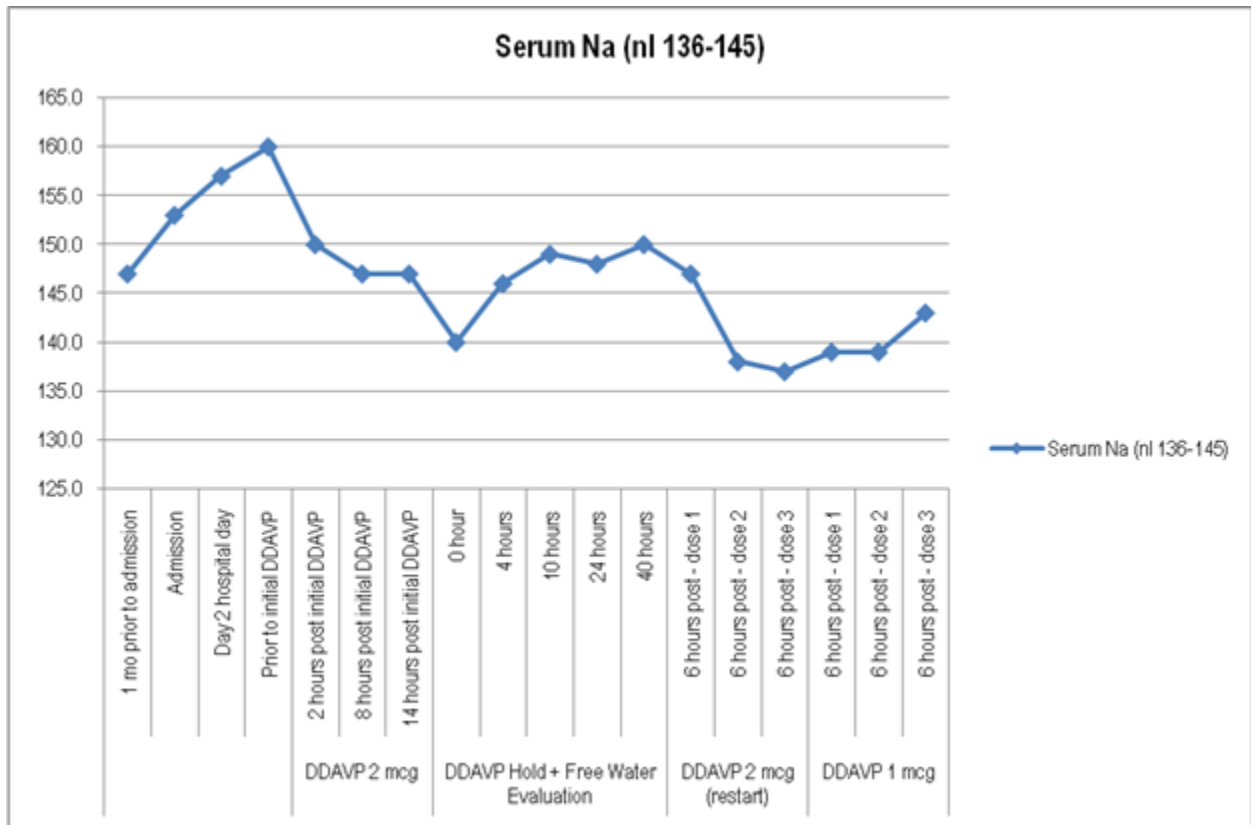
The treatment of choice is DDAVP intramuscular injection. Sublingual and nasal DDAVP have been proposed and used in the past with equal efficacy (7); IM DDAVP has been shown to be the treatment route in most cases described in literature as was done with our patient. The treatment route appeared to be determined at the discretion of the treating physician.
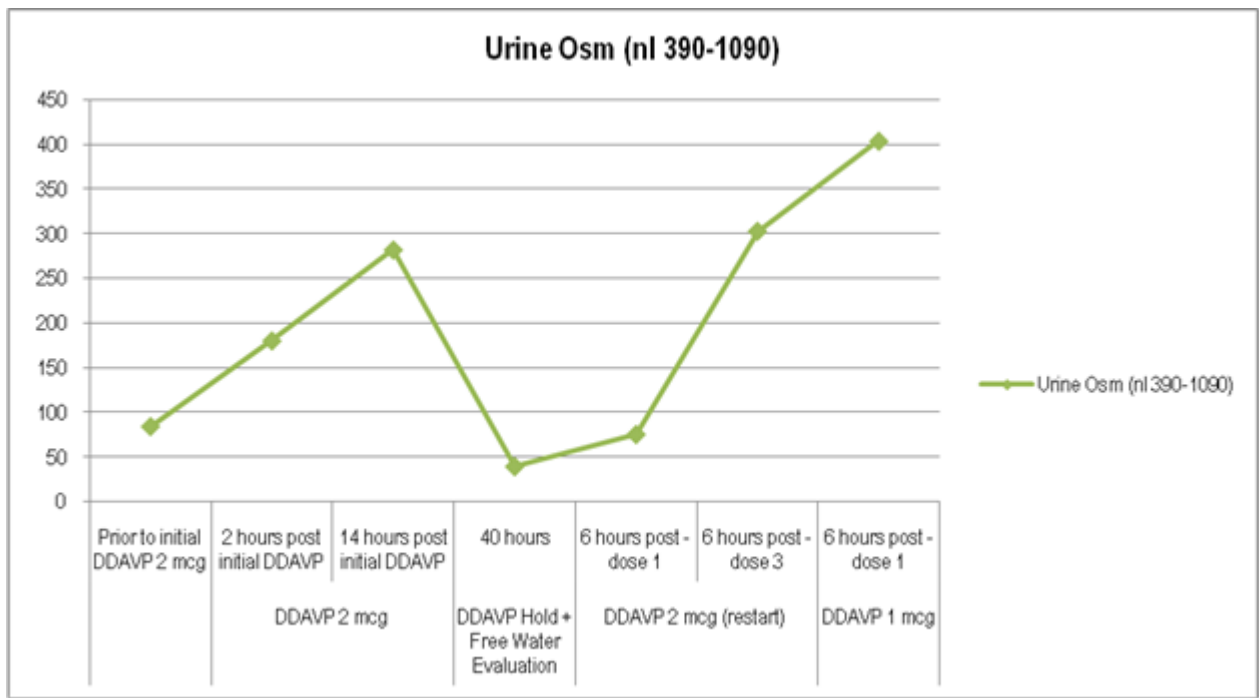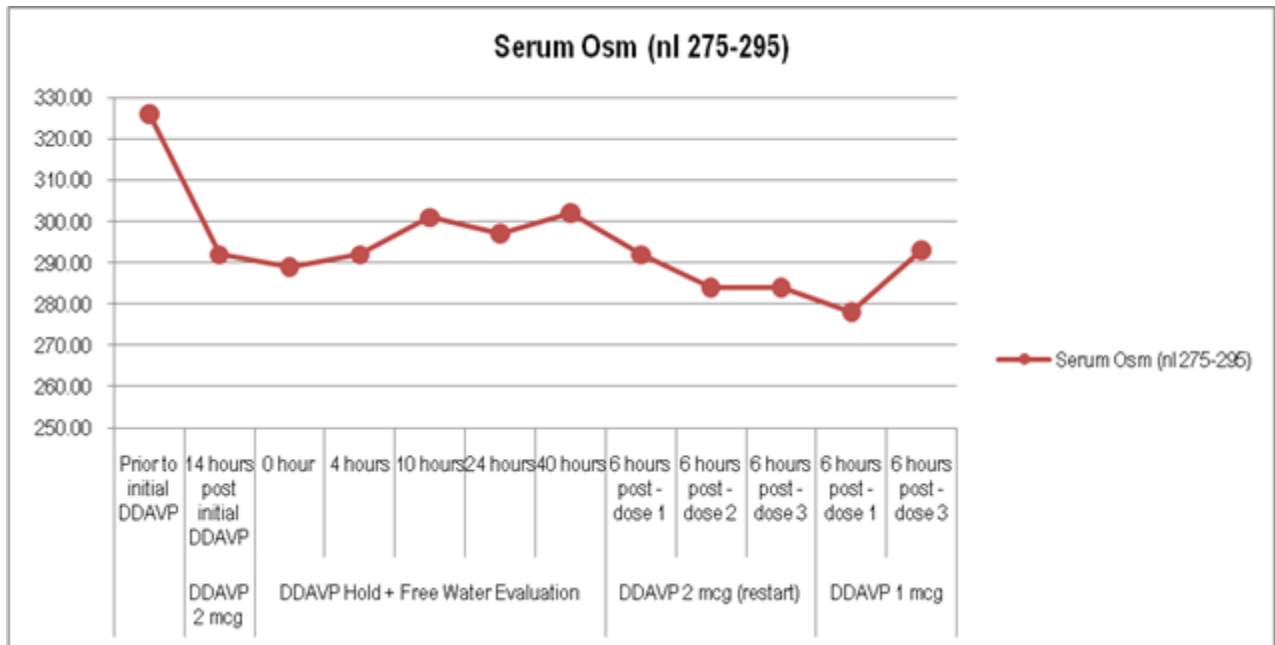
Although most cases of GDI resolve upon delivery of the infant, post-partum DI several months after delivery had been observed requiring extension of the DDAVP treatment until the resolution of the DI (8). In addition, recurrence of GDI has been reported in subsequent pregnancies (4). We also noted that in the literature there was an association between GDI and multiple gestations, preeclampsia, HELLP syndrome(Hemolysis, Elevated liver enzymes, Low Platelets) and acute fatty liver of pregnancy due to activation of hepatic vasopressinase (2,4). Pathological evaluation of a placenta demonstrated no histological difference between GDI and normal pregnancy (8). Close post-partum follow ups will be necessary to ensure resolution of GDI. We have advised the patient to return to clinic for management of any future pregnancies.

References

1. Petraglia F, D'Antona D. Maternal endocrine and metabolic adaptation to pregnancy. In UpToDate. Section Editors: Lockwood CJ, Snyder PJ. Deputy Editor: Barss VA. UpToDate, Waltham, MA, 2014.
2. Ananthakrishnan S. Diabetes Insipidus in Pregnancy: Etiology, Evaluation, and Management. (2009). Endocrine Practice. Vol 15(4): 377-382.
3. Aleksandrov N, Audibert F, Bedard MJ, Mahone M, Goffinet F, Kadoch IJ. (2010). Gestational Diabetes Insipidus: a Review of an Underdiagnosed Condition. JOGC. Vol 32(2): 225-231.
4. Hughes JM, Barron WM, Vance ML. (1989). Recurrent Diabetes Insipidus Associated with Pregnancy: Pathophysiology and Therapy. Obstetrics & Gynecology. Vol 73: 462-464.
5. Gordge MP, Williams DJ, Huggett NJ, Payne NN, Neild GH. (1995). Loss of Biological Activity of Arginine Vasopressin During Its Degradation by Vasopressinase form Preganancy Serum. Clinical Endocrinology. Vol 42: 51-58.

6. Yin-No Y, Kamiya Y, Okada M, Watanabe O, Ogasawara M, Fujinami T. (1998). Pregnant Woman with Transient Diabetes Insipidus Resistant to 1-Desamino-8-arginine vasopressin. Endocrine Journal. Vol 45(5): 693-696.
7. Laczi F, Mezei G, Julesz J, Laszlo FA. (1980). Effects of vasopressin analogues (DDAVP, DVDAVP) in the Form of Sublingual Tablets in Central Diabetes Insipidus. International Journal of Clinical Pharmacology, Therapy and Toxicology. Vol 18(2): 63-68.
8. Castiglione F, Buccoliero AM, Garbini F, Gheri CF, Moncini D, Poggi G, Saladino V, Rossi Degl'Innocenti D, Gheri RG, Taddei GI. (2009). Gestational Diabetes Insipidus: a Morphological Study of the Placenta. Pathologica. Vol 101: 227-229.

Serum Osm (nl 275-295)

Urine Osm (nl 390-1090)

Diagnostic Dilemma: A 41 year-old Man with Gastrointestinal Symptoms and an Unusual Exposure History

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Case Report

A 41 year-old previously healthy man was admitted with chief complaints of nausea, vomiting, diarrhea, and headache.

The patient was well until 10 days before admission when nausea, diarrhea, and headache developed suddenly. He experienced 1-3 episodes of emesis without solid components, blood, or bile staining and numerous loose but not watery stools per day. He denied melena, hematochezia, and mucus in the stool. He also reported fevers up to 102.3o F. and a 15-pound weight loss over 10 days. Two days prior to admission he received ciprofloxacin and metronidazole from his primary care provider for presumed community-acquired bacterial gastroenteritis without resolution of symptoms. Because of continued symptoms, he was evaluated in an Emergency Room at an outside hospital and transferred to this hospital.

He had a past medical history significant for hypertension and depression. His social history was remarkable for occupational exposure to domestic and exotic livestock (cheetahs, monkeys, zebras, and birds) through his job at a sale barn for several weeks prior to admission. In addition, he had been exposed to bovine placenta through birthing calves at his farm. He denied sick contacts, tick bites, and environmental exposure to chemicals.

On arrival, physical exam was remarkable for tachycardia without postural changes in blood pressure, good perfusion, and decreased breath sounds at the right lung base. Laboratory studies were remarkable for leukocytosis (WBC 10,400/mm3 with 84.4% granulocytes) and mild transaminitis (AST 67 U/L, alkaline phosphatase 140 U/L). A chest x-ray revealed right lower lobe consolidation and a chest CT scan revealed right lower lobe pneumonia with associated mediastinal lymphadenopathy. A 2 liter normal saline bolus was administered, and he was started on ondansetron for nausea. Diagnostic testing was ordered.

Discussion

This 41 year-old previously healthy patient presented with symptoms of gastroenteritis and headache and was subsequently found to have a lobar pneumonia, fever, and transaminitis. His occupational exposure to exotic animals and products of bovine conception suggested an uncommon cause of his symptoms.

Q fever, caused by the intracellular bacterium Coxiella burnetii, can result in fever, atypical pneumonia, night sweats, and hepatitis and is associated with contact (most commonly via aerosolization and inhalation) with products of conception from infected cattle, sheep, and goats (placenta, reproductive fluids). Other modes of transmission include tick bites, consumption of unpasteurized milk products from infected animals, and, rarely, person-to-person transmission. One hundred thirty one cases of Q fever were reported in the United States in 2010. In Missouri, the annual reported incidence was 0.4-1.0 cases per million (CDC data). Q fever is a diagnosis of particular interest due to its potential use as a weapon of bioterrorism related to its resistance to physical stress and ability to aerosolize and travel long distances (up to 10 miles in some reported cases) (1-3).

Brucellosis is another zoonotic infection associated with contact with infected products of bovine conception. Following infection by Brucella spp, brucellosis may cause undulating fever, constitutional symptoms, arthralgias, neuropsychiatric symptoms, gastrointestinal symptoms, cough, dyspnea, and endocarditis. The most common mode of transmission is through consumption of unpasteurized milk and milk products from infected animals. Currently, fewer than 100 cases are reported to the CDC annually, the majority from California, Florida and Texas (CDC data). Although B. abortus and B. suis species are the most common species in North America, the majority of human cases result from the bacterium B. melitensis, which has the highest pathogenicity of the species and whose typical reservoir is sheep (4).

Although the patient denied tick exposure, his occupational exposure to domestic and exotic livestock and living arrangements on a farm place him at higher risk for tick-borne illnesses such as ehrlichiosis. Symptoms of ehrlichiosis may include headaches, myalgias, fatigue, nausea, and in rare cases a macular, maculopapular, or petechial rash on the trunk, legs, arms, and face. If left untreated, late infection may result in a toxic shock-like syndrome, likely due to up-regulation of TNF-alpha (5-6).

Based on the patient's exposure history, psittacosis was also considered. Infection with the bacterium Chlamydia psittaci in humans often results from inhalation of aerosolized feces or contact with respiratory secretions of infected birds. Clinical manifestations of acute infection include flu-like symptoms, productive cough, and hemoptysis. However, gastrointestinal symptoms and transaminitis are not typically a prominent feature of infection with C. psittaci (7).

With the acute onset of symptoms and transaminitis, we considered viral hepatitis as well as community-acquired infection with Clostridium difficile, although C. difficile would not account for his respiratory symptoms. In addition, antibiotic therapy with metronidazole from his primary care provider would likely have treated infection with C. difficile. Finally, other common causes of atypical pneumonia and gastroenteritis were considered, including Legionnaire's disease, giardiasis, cryptosporidiosis, and histoplasmosis.

Finally, the patient had a history of psychiatric illness, so self-induced illness was considered. However, the patient's depressive symptoms were well-controlled, and he had no prior suicide attempts. In addition, a self-induced illness would likely not account for the combination of gastrointestinal and respiratory symptoms, making self-induced sequelae of his psychiatric illness less likely.

Case Report, continued

Results of diagnostic laboratory testing are as follows:

Comprehensive Urine Drug Screen Negative	
Hepatitis B surface Ag	Nonreactive
Hepatitis B core Ab IgM	Nonreactive
Hepatitis C Ab by EIA	Nonreactive
Hepatitis A Ab IgM	Nonreactive
Urine Histoplasma Ag	Negative
C. burnetii Phase I IgG	<1:16
C. burnetii Phase II IgG	(H) 1:16
Brucella Ab	<1:20
Ehrlichia IgG	<1:64
Ehrlichia IgM	<1:16
C. psittaci IgG	1:256
C. psittaci IgM	<1:10
C. difficile PCR	Negative
Cryptosporidium	Negative
Giardia Ag by EIA	Negative
Stool ova and parasites	Negative

The patient experienced prompt resolution of his gastrointestinal symptoms and pneumonia following antibiotic therapy with azithromycin and doxycycline. He was discharged on hospital day 3 with azithromycin and doxycycline. He was asymptomatic one week after discharge.

Conclusion

We report the case of a 41 year-old previously healthy man with nausea, vomiting, and diarrhea who was subsequently found to have fever, lobar pneumonia, transaminitis, and an unusual exposure history. Although serological testing was equivocal, the patient's clinical presentation, response to antibiotic therapy, and exposure history are consistent with the diagnosis of Q fever. This case provides an example of diagnosis based on integration of clinical presentation, history, and response to therapy when laboratory testing may be equivocal. In the case of this patient with an unusual exposure history, the medical team's final diagnosis was based on his clinical presentation, exposure history, serologic testing, and response to therapy. Careful history,

physical examination, and clinical course remain the principal components of differential diagnosis complemented by additional laboratory testing.

References

1. Tissot-Dupont H, Torres S, Nezri M, Raoult D. Hyperendemic focus of Q fever related to sheep and wind. Am J Epidemiol 1999;150:67–74.
2. Tissot-Dupont H, Amadei MA, Nezri M, Raoult D. Wind in November, Q fever in December. Emerg Infect Dis 2004;10:1264–9.
3. O'Connor BA, Tribe IG, Givney R. "A windy day in a sheep saleyard: an outbreak of Q fever in rural South Australia." Epidemiol Infect. 2014 May 9:1-8. [Epub ahead of print].
4. Franco MP, Mulder M, Gilman RH, Smits HL. Human brucellosis. Lancet Infect Dis. Dec 2007;7(12):775-86.
5. Marty AM, Dumler JS, Imes G, Brusman HP, Smrkovski LL, Frisman DM (August 1995). "Ehrlichiosis mimicking thrombotic thrombocytopenic purpura. Case report and pathological correlation". Hum. Pathol. 26 (8): 920–5.
6. McBride, Jere W.; Walker, David H. (31 January 2011). "Molecular and cellular pathobiology of Ehrlichia infection: targets for new therapeutics and immunomodulation strategies". Expert Reviews in Molecular Medicine 13.
7. Smith KA, Bradley KK, Stobierski MG, et al. Compendium of measures to control Chlamydophila psittaci (formerly Chlamydia psittaci) infection among humans (psittacosis) and pet birds, 2005. J Am Vet Med Assoc. Feb 15 2005;226(4):532-9.

Editorial: Impact of Academic Hospitalists on American Medical Education: A Compact Review

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Introduction

Hospitalists are physicians whose medical practice focuses on general medical inpatient care. (1) Wachter and Goldman first used the term *Hospitalist* in 1996 to describe a new type of physician in the United States. (2) Initially, the concept of the Hospitalist was not widely accepted and faced significant resistance from many physicians. (3) However, Hospitalists now constitute a major force in the healthcare industry, providing inpatient care in both non-teaching settings as well as teaching hospitals ranging from small community hospitals to large academic centers. This article will discuss the role of academic Hospitalists in medical education in the United States.

Discussion

Traditionally, general Internal Medicine faculty has been responsible for resident physician and medical student education. However, it is becoming increasingly more common for academic Hospitalists to serve as core teaching faculty at community and university hospitals. (7) Many studies have demonstrated the benefit of using Hospitalists as teaching faculty in the domains of resident education, resident satisfaction, improved teaching, and higher quality of teaching rounds. (1, 4, 5) Similarly, medical student education has also significantly benefited from academic hospitalist faculty. (6)

One of the initial studies by Chung et al assessing the effectiveness of academic Hospitalists in medical education indicated significant satisfaction among house staff on Hospitalist teaching rounds. Highlights of that study, published in the American Journal of Medicine, are summarized below. (5)

- 336 end-of-month surveys and 201 year-end surveys were sent to the 86 residents. A 23-point questionnaire was used. Response rates were 53% and 58%, respectively. Overall, 75% of residents responded to at least one of the two surveys. Residents in each of the comparison groups did not differ with regard to year in training, age, or sex.
- In the end-of-month survey, Hospitalist service resident physicians were more satisfied than traditional service residents (59% vs. 38%, P = 0.10) on inpatient teaching rounds.
- In the year-end survey, resident physicians who experienced both the Hospitalist and traditional non-Hospitalist teaching services preferred the Hospitalist service in inpatient teaching rounds (P = 0.05).
- Resident physician preference for the Hospitalist service was evident in the educational realm, with surveyees indicating better learning experience, more educationally stimulating work, greater emphasis on education by the attending physician, and higher quality of attending rounds. When asked which service they would choose if given the opportunity, 72% of residents selected the Hospitalist service.
- Some initial concerns regarding Hospitalist services at teaching hospitals included the worries that a Hospitalist service would inappropriately limit autonomy (28%) and compromise exposure to different faculty members and teaching styles (60%). However, most resident physicians surveyed emphasized that the educational advantages of full-time attending physician presence outweighed those concerns.

In addition to resident physician education, Hospitalist teaching in academic settings has a tremendous impact on medical student education. Hunter et al reported the results of a study in

Academic Medicine describing medical student evaluation of Hospitalist versus non-Hospitalist teaching rotations. This study found that academic Hospitalist teaching rounds provided unique benefits over non-Hospitalist rotations, including expertise in inpatient medicine, accessibility of Hospitalists to students, emphasis on continuity of care, demonstration of effective communication, and representation of a realistic practice style in a managed care setting. (6) The students surveyed also emphasized that academic Hospitalists helped cultivate awareness of issues such as cost effectiveness and systems-based improvements in areas such as patient follow-up, communication with primary care physicians post-acute care, and palliative care. (6) Disadvantages mentioned by the medical students included reduced patient length-of-stay with fewer opportunities for students to follow the natural history of patients' illnesses, marginalization of the primary care physician, division of inpatient versus outpatient medicine, and decreased exposure to subspecialists, primary care physicians, and physician–scientists. (6)

More recently, Beasley et al surveyed all 386 Internal Medicine residency directors in the United States in 2005 (272 respondents) and 2007 (236 respondents) regarding attitudes towards academic Hospitalists. Results of this study, published in the Journal of Hospital Medicine, demonstrated that the majority of Internal Medicine residencies have recruited Hospitalists to provide teaching rounds, lectures, and bedside teaching in community and university hospitals. In addition, a small number of institutions have developed Hospitalist fellowship training programs to promote the position of Hospitalist as a career option for graduates. (7)

Conclusion

Since the introduction of Hospitalist services in the American health care industry in 1996, the position has grown rapidly and become a vital service in the inpatient care setting. More recently, the trend of hospitalist-run preoperative and transitions-of-care clinics has emerged across the United States. The role of the Hospitalist in the medical education is undeniably significant, suggesting that the future of medical education will include more academic Hospitalists and will take place in academic centers.

References

1. Pressem DM. Hospitalists in medical education: coming to an academic medical center near you. Nat'l Med Assoc. 2006 Sep; 98(9):1501-4.
2. Wachter RM, Goldman L. The emerging role of "hospitalists" in the American health care system. N Engl J Med. 1996; 335:514–7.
3. Brown RG. Hospitalist concept: another dangerous trend. Am Fam Physician. 1998;58:339–42
4. Hauer KE, Wachter RM, McCulloch CE, Woo GA, Auerbach AD. Effects of hospitalist attending physicians on trainee satisfaction with teaching and with internal medicine rotations. Arch Intern Med. 2004; 164:1866-71.
5. Chung P, Morrison J, Jin L, Levinson W. Humphrey H. Meltzer D. Resident satisfaction on an academic hospitalist service: Time to teach. Am J Med. 2002; 112: 597-601.

6. Hunter AJ, Desai SS, Harrison RA, Chan BK. Medical student evaluation of the quality of hospitalist and non-hospitalist teaching faculty on inpatient medicine rotations. Acad Med. 2004; 79:78-82.
7. Beasley BW, McBride J, McDonald FS. Hospitalist involvement in internal medicine residencies. J Hosp Med. 2009 Oct; 4(8):471-5.

Review Article: Care of the Hospitalized Patient with Cystic Fibrosis: A Summary of Current Practice Guidelines; Recommendations for the Hospitalist, Part 2

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In a short review of our last discussion, I will remind the reader that cystic fibrosis is a complex genetic disease affecting many organs, but it is often lung disease that brings the patient to our attention. The natural history of lung disease begins with the production of abnormal mucus (a result of the gene mutations associated with this disease). We refer to a vicious cycle of disease, including early and persistent infection of the airway, concomitant inflammatory response, and, over time, progressive airway obstruction. These processes ultimately result in respiratory failure. As disease worsens there is an increased likelihood of respiratory complications. In addition, patients with cystic fibrosis often present with multiple manifestations of disease upon presentation to the hospital, complicating assessment and management. This second installment of recommendations for the hospitalist will briefly address these complications to assist in the management of these patients.

The cystic fibrosis care team often acts as the gate keeper for hospital admissions given the specialized ability to recognize a pulmonary exacerbation. However, patients may present to the emergency department with symptoms requiring urgent attention, such as massive hemoptysis or pneumothorax. The following recommendations are summarized from guidelines provided by the Cystic Fibrosis Pulmonary Therapies Committee. The CF Foundation pulmonary therapies committee consists of a multi-disciplinary group including representative physicians, nurses,

respiratory therapists, physical therapists, pharmacists, CF families and CF Foundation staff. High volume cystic fibrosis centers participated in a questionnaire, a literature search was performed, and an expert panel reviewed all of the data collected. This information was brought to the committee for review with eventual creation of these guidelines following group consensus.

Hemoptysis:

Hemoptysis is a common symptom in patients with CF; therefore it is important for care providers to inquire about bleeding in the outpatient setting. The literature indicates that about 9% of patients report hemoptysis , which the author estimates to be the average at this center as well. Often there is scant-to-moderate bleeding, described as streaks or spots in the sputum. However, on occasion the patient will describe a large volume of blood. It is known that massive, life-threatening bleeding can occur. The literature indicates 4% of all patients with cystic fibrosis will suffer a massive hemoptysis during his or her lifetime. Frequently patients have difficulty in defining the volume of blood. The author is able to recall only one patient with an accurate measurement. While driving his car, he reported an episode of hemoptysis where he coughed up blood into his coffee cup and filled it to approximately 8 ounces. However, patients often expectorate into the sink or the toilet making volume estimation difficult. The patient may overestimate volume, particularly if it is his or her first episode of hemoptysis. Based on volume of expectorate, other symptoms, and circumstances surrounding the hemoptysis, we elect either to monitor or treat. We have asked our patients to contact us with (1) The first episode of hemoptysis, and (2) Expectorated blood greater than a teaspoon with or without changes in pulmonary symptoms.

We also would recommend treatment if patient has other pulmonary symptoms with ongoing small-volume hemoptysis (greater than 5 ml, but less than 50 ml). Treatment may consist of oral antibiotics at home but may also require an admission to hospital. We prefer to observe and evaluate patients with hemoptysis of 50-250 mL, even if they do not have other pulmonary symptoms.

The patient with massive hemoptysis should always be admitted to the hospital. This can be life-threatening.

Admission recommendations include:

1. Discontinue any NSAIDs;
2. Hold nebulized hypertonic saline;
3. Administer vitamin K to correct possible deficiency (recall that CF patients often experience malabsorption of fat soluble vitamins);
4. Treatment for pulmonary bacterial colonization in patients with changes in sputum, increased cough, or other symptoms suggestive of a pulmonary exacerbation. Recall Pseudomonal infection is treated with two anti-pseudomonal medications (with a consult to the cystic fibrosis team);
5. Continue airway clearance including chest physiotherapy with vest, bronchodilators, Pulmozyme, and/or inhaled antibiotics. We recognize that mucus

plugging and the resulting inflammation of the airway is likely the etiology of the bleeding; therefore we will need to address this. However, we may hold IPV and if bleeding continues or increases, consider holding Pulmozyme first and then other modalities for short time until bleeding subsides;

6. In the case of massive hemoptysis, we like to alert the bronchoscopy lab, Intensive Care Unit, and Interventional Radiology in case of acute decompensation. In addition, therapies that should be withheld include BiPAP, airway clearance therapies, all other inhaled medications, and NSAIDs. Vitamin K should still be administered. Pulmonary function testing should be held until significant bleeding has subsided.

Pneumothorax:

According to the literature, the average and annual incidence of pneumothorax is 0.64% or one in 167 patients per year. Along with hemoptysis, pneumothorax occurs more commonly in older patients with advanced disease. The author can recall only one pneumothorax in the past eight years of practice, occurring in a patient just before the time of her transplant who suffered pneumothorax while traveling to Denver by airplane.

1. Patients with a large pneumothorax should be admitted to the hospital, but those with small pneumothoraces who are clinically stable may be closely observed in an outpatient setting.
2. The patient with large pneumothorax should have a chest tube placed.
3. The patient with first pneumothorax should not go undergo pleurodesis. However patients with recurrent large pneumothoraces should undergo pleurodesis to prevent recurrence. The preferred method is surgical pleurodesis.
4. Since pneumothoraces typically occur in patients with advanced obstructive airways disease, one could argue for treatment with antibiotics: however, there is no consensus on this issue.
5. BiPAP should be withheld from patients with pneumothorax as long as the pneumothorax is present.
6. The patient with pneumothorax should not fly in a plane, not lift weights, and should not perform spirometry for 2 weeks after the pneumothorax has resolved.
7. Mechanical airway clearance methods such as Intrapulmonary Percussive Ventilation and Positive Expiratory Pressure (PEP) should be held in large pneumothorax, but there is no consensus on withholding vest or CPT.
8. Inhaled airway treatments should NOT be held unless cough is more severe with them.

GI spectrum of Constipation-Obstipation-DIOS (Distal Intestinal Obstructive Syndrome):

Complete or incomplete intestinal obstruction occurs when there is accumulation of viscous fecal material combined with sticky mucoid intestinal content, which adheres to the intestinal wall of the terminal ileum and proximal colon. DIOS is another common complication in cystic fibrosis. A significant mass of material may be interwoven and connected to the crypts and villi of the distal intestine and may prove difficult to remove. In many cases, this is a chronic

condition that can be aggravated intermittently. It may occur with a wide range of severity. Some incomplete obstruction cases may go unnoticed by the CF care team when patients assume they had a transient "GI bug" that resolved without medical intervention. Again, these complications seem to occur more often in adults than children, more frequently in pancreatic-insufficient patients (although occurs in pancreatic sufficient patients as well), and in post-transplant patients.

In constipation, the bowel symptoms and imaging indicate a long-standing condition. Fecal material is distributed throughout the colon. In DIOS, there is a right lower quadrant mass that may be palpable and is also seen on a plain film of the abdomen. It may present acutely or sub-acutely with intermittent abdominal pain associated with abdominal distention.

The phenomenon is again the result of the abnormal gene product CFTR (Cystic fibrosis Transmembrane Conductance Regulator). This is the same chloride channel found in lung epithelium, where chloride secretion and sodium absorption are the driving force for fluid secretion into the lumen. In the lung, a non-functional chloride channel causes dehydration of the mucus and subsequent plugging of small airways. In the intestine, abnormalities in the mucus also predisposes to obstruction. In addition, other factors influence the viscosity of luminal contents and gut motility. Inflammatory processes are theorized to contribute to neuromuscular dysfunction. Intestinal wall thickening has been seen involving the muscularis mucosa. Hypertrophy may be the consequence of dysmotility as well as the effect of viscid intestinal contents.

Risk factors for the development of GI problems include dehydration precipitated by illness (such as a pulmonary exacerbation), dehydration associated with hot weather, and CF-related diabetes which may alter hydration status.

Treatment for this GI spectrum includes oral rehydration combined with stool products for mild, incomplete obstruction or constipation. Osmotic laxatives, which draw more fluid into the intestinal lumen, are the most effective and best tolerated. Gut lavage with balanced electrolyte solutions and intravenous fluids are rarely required. Care should be taken to avoid rapid fluid shifts. We attempt to avoid dehydration and optimize enzyme dosing to decrease the risk of recurrence. Some patients seem to do better with prophylactic osmotic laxative therapy.

CF-Related Diabetes (ESRD):

CFRD is the most common comorbidity in cystic fibrosis and occurs in 40-50% of adults. The disease has features of both type I and type II diabetes mellitus; however it is a clinically distinct phenomenon. The primary cause is insulin insufficiency due to damage to the pancreas. However, fluctuating levels of insulin resistance also occur and are related to chronic inflammation with acute intermittent illnesses. Diagnosis is generally not made during acute hospitalization for pulmonary exacerbation or other illness but rather during a time of stable health.

Because the main pathology in CFRD is insulin insufficiency, the treatment is insulin. There is clear evidence that patients with insulin therapy who achieve good control of blood sugars also

demonstrate improvements in weight, protein anabolism, pulmonary function, and survival. There is no single proven insulin regimen, and each case requires individualized attention. CFRD patients still produce some endogenous insulin and except during acute illness, insulin needs are often low such as the case with type I diabetes in the so-called "honeymoon period." It is during an acute illness or with oral steroid therapy that insulin requirements may steeply rise. Once the illness resolves, it may take 4-6 weeks for insulin requirements gradually to return to baseline.

The goals of glucose management are the same as ADA recommendations for all patients with diabetes. Hemoglobin A1c values less than 7% are the usual target. However, hemoglobin A1C is often low in cystic fibrosis patients secondary to an increased rate of turnaround in red blood cells.

As you may recall from our first article, meeting nutrition requirements is essential in the management of this disease. Adequate caloric intake to maintain target BMI is critical to health and survival in cystic fibrosis patients. Therefore those patients with CFRD should NOT decrease calorie intake. These patients require a very high calorie diet that is usually 120-150% of the recommended daily intake for age. This is because there is increased resting energy expenditure with increased work of breathing and there is increased loss of calories through malabsorption.

CF evidence-based guidelines also recommend exercise for its benefit to overall health, cardiovascular fitness, and pulmonary clearance. Virtually all cystic fibrosis patients, even those with severe pulmonary disease, are capable of participating in strength training and aerobic exercise.

Cystic Fibrosis "Pearls "

– Cystic fibrosis is a progressive genetic disease, marked by episodes of pulmonary exacerbation

– Treatments are based on pathophysiology

– Airway clearance, nutrition, and antibiotics are key elements to manage in treatment

– A patient's "usual" or home oral antibiotics are NOT stopped upon presentation to hospital for intravenous antibiotics

– Examples of treatments to promote airway clearance include bronchodilators, mucolytic agents, mucus hydration agents, inhaled antibiotics and mechanical clearance (vest, IPV, accapella, coronette, aerobika etc)

– Give CF patients vitamin K for hemoptysis

– Think about airway effects when considering treatments for patients with both hemoptysis and pneumothorax

– Antibiotics should be considered whenever there is a change in pulmonary symptoms; Pseudomonas is treated with two agents with different mechanisms of action

– Most cystic fibrosis patients have some degree of constipation and bowel management is always with osmotic agents

– Do not put CFRD patients on a calorie restricted diet

– Do not put CF patients on a salt-restricted diet

Resources:

1. Flume P, Mogayzel P, Robinson K, Rosenblatt R, Quittells L, Marshall B and the Clinical Practice Guidelines for Pulmonary Therapies Committee. Cystic Fibrosis Pulmonary Guidelines, Pulmonary Complications: Hemoptysis and Pneumothorax. American J of Respiratory and Critical Care Medicine Vol. 182 2010.
2. Moran A, Brunzell C, Cohen R, Katz M, Marshall B, Onady G, Robinson K, Sabadosa K, Stecenko A, Slovis B The CFRD Guidelines Committee. Clinical care guidelines for cystic fibrosis-related diabetes: A position statement and American diabetes Association and the clinical practice guideline of the cystic fibrosis Foundation, endorsed by the pediatric endocrine Society; Diabetes care, vol 33, no 12, December 2010: pp 2697-2708
3. Colombo C, Ellemunter H, Houwen R, Munck A, Taylor C, Wilschanski M. Guidelines for the diagnosis and management of distal intestinal obstruction syndrome in cystic fibrosis patients. J of Cystic Fibrosis, vol 10 suppl 2 (2011) S24-S28
4. Cystic Fibrosis Foundation website: cff.org

ASK A SPECIALIST: ASK A PATHOLOGIST

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Question:

I ordered a type and screen on my patient, and the blood bank reported that her direct Coombs test was positive. Does that mean my patient has autoimmune hemolytic anemia?

Answer:

The Direct Coombs test, also called the Direct Antiglobulin Test (DAT), is performed by adding reagent antibodies against human IgG and complement, also known as anti-human globulin or Coombs reagent, to the patient's red blood cells. The test is positive if the antibodies cause the red blood cells to agglutinate, indicating that IgG antibodies and/or complement are bound to the surface of the patient's red blood cells in vivo.

The DAT is an extremely sensitive test, and can detect as few as 100 IgG molecules per red blood cell. In comparison, red blood cells from healthy, non-anemic patients generally have less than 60 IgG molecules bound to the surface. The DAT is routinely performed in the blood bank as part of the routine workup for positive antibody screens and after transfusion reactions; the test is also useful in neonates with suspected hemolytic disease of the fetus and newborn and in the evaluation of patients with suspected immune-mediated hemolysis.

A positive DAT alone is not diagnostic of immune mediated hemolysis. Up to 15% of hospitalized patient specimens may have a positive DAT, often as a reactive phenomenon in patients with increased IgG levels due to infection, inflammation, or malignancy. A positive DAT in a patient with no evidence of hemolysis or recent transfusions does not generally require any additional testing.

If the patient does have clinical evidence of hemolysis such as decreasing hemoglobin with elevated LDH, low haptoglobin, or microspherocytes on peripheral smear, a positive DAT suggests that the hemolysis may be immune-mediated. Immune-mediated hemolysis may be caused by warm autoimmune hemolytic anemia, cold agglutinin diease, paroxysmal nocturnal hemoglobinuria, or drug-induced hemolytic anemia.

In a patient with a positive DAT, ask the following questions:

1. Has the patient been recently transfused? If so, consider an acute or delayed hemolytic transfusion reaction.
2. Does the patient have clinical evidence of hemolysis? If so, consider causes of immune-mediated hemolysis.
3. Is the patient receiving drugs which can cause a positive DAT? The list is long, but includes IVIG, RhoGam, penicillins, cephalosporins, procainamide, and many others.
4. Has the patient received a marrow or organ transplant? Passenger donor lymphocytes may produce antibodies against the recipient's red blood cell antigens.

References:

1. Zantek ND, Koepsell SA, Tharp DR, et al. The direct antiglobulin test: A critical step in the evaluation of hemolysis. American Journal of Hematology. 2012;87(7):707-709.
2. Richa E, Benidt G, Tauscher C, et al. Eluate testing following microscopically positive direct antiglobulin tests with anti-IgG. Annals of Clinical and Laboratory Science. 2007;37(2):167-169.
3. Heddle NM, Kelton JG, Turchyn KL, et al. Hypergammaglobulinemia can be associated with a positive direct antiglobulin test, a nonreactive eluate, and no evidence of hemolysis. Transfusion. 1988;28(1):29-33.

Clinical Vignettes: HIV associated Lymphoma

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Questions:

Part 1: A 25-year-old HIV-positive male presents with a four day history of fever and headache. The headache is a dull pain that acutely worsens with coughing. It is unassociated with photophobia, phonophobia, or vision changes, but worsens with fever spike. It is different than the headaches he had when diagnosed with Mollaret's meningitis a month ago and he denies neck stiffness. He also reports fever and night sweats. He denies symptoms of sinusitis. He is not currently being treated for HIV and a month ago his CD4 count was 163 cells/mm^3 and viral load was 196,000 copies/ml. On exam, he has cervical, supraclavicular, axillary and inguinal lymphadenopathy. Head CT was normal. A subsequent cervical lymph node biopsy was performed which reveals large, bi-nucleate cells with inclusion-like nucleoli. A computerized tomography (CT) of the chest, abdomen, and pelvis discovered multiple mesenteric lymph nodes. What type of cancer is the most likely diagnosis?

1. A)Hodgkin lymphoma
2. B)Burkitt lymphoma
3. C)Follicular lymphoma

4. D)Primary central nervous system lymphoma

Part 2: A PET scan was subsequently performed 2 months later and FDG-avid lesions were noted in the small bowel and the left testicle. An exploratory laparotomy was performed, resulting in small bowel resection and left partial orchiectomy. Two weeks later, he returns with a headache and left sided ptosis. MRI brain revealed a large extra axial mass lesion measuring 6.2 cm x 3.0 cm x 6.4 cm in the left temporo-parietal region resulting in a mass effect and 2 mm midline shift. He undergoes a craniotomy with excisional biopsy and duraplasty for a large defect. Pathology from all the three locations mentioned above reveals primarily basophilic cells interspersed with histiocytes with abundant cytoplasm ("starry night"). What is the most likely diagnosis?

1. A) Hodgkin lymphoma
2. B) Burkitt lymphoma
3. C) Follicular lymphoma
4. D) Primary central nervous system lymphoma

Part 1: A

Explanation: Primary central nervous system lymphoma is ruled down because it is most common in patients with a CD4 count <50 cells/mm^3 and typically presents as CNS mass lesions with seizures and altered mental status. Non-Hodgkin lymphomas (NHL) are AIDS-defining cancers that are very common in HIV+ patients and commonly presents with diffuse lymphadenopathy; however, NHL does not have Reed-Sternberg cells as seen on the biopsy. Burkitt lymphoma typically presents as an extra-nodal tumor mass, which was not seen on imaging. Hodgkin lymphoma, though not an AIDS-defining malignancy, is usually common in moderately immunosuppressed patients rather than severely immunosuppressed patients, and this is consistent with the Reed-Sternberg cells seen on biopsy. Therefore, answer A is the best choice.

Part 2: B

Explanation: Hodgkin lymphoma rarely enters the testicles or CNS, which rules it down significantly, despite the previous diagnosis of Hodgkin lymphoma. Now that several extra nodal masses have been identified and have been shown to have the characteristic "starry sky" appearance, Burkitt lymphoma is much more likely.

Thiamine Deficiency: A Case Presentation and Literature Review

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Abstract

This case examines the complicated hospital course of a patient ultimately diagnosed with thiamine deficiency. The presentation, diagnostic work up, and treatment of a 53-year-old male with a history of schizoaffective disorder, pituitary adenoma status post trans-sphenoidal adenectomy, GERD, hyperlipidemia, and glaucoma are evaluated. He had lived at a care facility for over 10 years, and he was brought to an outside hospital after members of the staff found him in bed, unresponsive. They also had concerns about a one-day history of inability to sit or stand up straight and gait abnormalities. An extensive work up with chest x-ray, EKG, urinalysis, routine CBC and CMP, blood and urine cultures, head CT, MRI of the brain and spine, lumbar puncture, EEG, and various miscellaneous labs ensued. Urinalysis and urine cultures revealed evidence of Enterococcus urinary tract infection. EEG revealed evidence of encephalopathy. The patient was also hyponatremic with thiamine and pyridoxine deficiency. Thiamine deficiency was diagnosed after a dramatic improvement in gait and mentation after administration of thiamine.

Introduction

Thiamine or vitamin B1 is an essential water-soluble vitamin found in yeast, organ meat, pork, legumes, beef, whole grains, and nuts. It functions in energy generation by participating in decarboxylation of alpha-ketoacids and branched-chain amino acids. It also functions in peripheral nerve conduction through an unknown mechanism. The most common cause of thiamine deficiency worldwide is poor dietary intake. In developed countries, the most common causes are alcoholism and chronic disease (i.e. cancer). Other patients at risk include patients with poor nutritional status on parenteral glucose, patients after bariatric bypass surgery, pregnant patients with prolonged hyperemesis gravidarum, and patients on chronic diuretic therapy due to urinary losses.[1] Thiamine deficiency due to overuse of the vitamin within the body can occur in hyperthyroidism, pregnancy, lactation, or fever. Severe liver disease can impair the utilization of thiamine leading to a similar clinical picture.[3]

Early stages of thiamine deficiency manifest as anorexia and nonspecific symptoms including irritability and decreased short-term memory. When thiamine deficiency persists, patients will progress to a condition called beriberi, which is classified as wet or dry with frequent overlap between the two. Symptoms of wet and dry beriberi are pain and paresthesia. Dry beriberi presents with peripheral neuropathy of the motor and sensory systems with diminished reflexes, especially in the lower extremities. Patients with wet beriberi will also have cardiovascular manifestations such as cardiomegaly, tachycardia, high-output congestive heart failure, peripheral edema, and peripheral neuritis.[1]

Thiamine deficiency is associated with alcoholism in 90% of cases in developed countries. Alcoholic patients most commonly present with Wernicke's encephalopathy due to thiamine deficiency. Wernicke's encephalopathy is associated with a classic triad of ophthalmoplegia, cerebellar ataxia and mental impairment. However, all three, if any, of the classic signs are not often seen in patients with Wernicke's encephalopathy. Wernicke-Korsakoff syndrome is diagnosed when there is also an inability to form new memories and confabulatory psychosis. While Wernicke-Korsakoff syndrome is highly associated with alcoholism, patients with thiamine deficiency due to other causes can be diagnosed with the syndrome as well.[2]

Patients with suspected thiamine deficiency are managed with 100mg/d of IV thiamine for seven days, and 10mg/d orally everyday thereafter until there is resolution of symptoms.[1] A maintenance dose of 2.5-5 mg per day is then recommended.[3] Treatment with IV and oral thiamine is very safe, with minimal to no risk.[2] It is important to begin thiamine replacement early if thiamine deficiency is suspected, because of risk for morbidity due to permanent psychosis.[2] Administration of thiamine can even be used as a diagnostic test in cases of acute heart failure or insidious peripheral neuropathy, because of the rapid and dramatic improvement in symptoms if deficiency truly exists. Prognosis is good for patients with thiamine deficiency that has not progressed to Korsakoff syndrome.[3] In Wernicke-Korsakoff syndrome, psychosis may not improve for months and may be permanent.[1]

 Case Presentation

History: S.M. is a 53-year-old male with a past medical history of schizoaffective disorder, pituitary adenoma status post trans-sphenoidal adenectomy, GERD, hyperlipidemia, and glaucoma. He presented to an outside hospital due to altered mental status and muscle weakness. History was obtained from the patient and from reports from the care facility he has lived in for over 10 years. The care facility reported that the patient had a one-day history of problems sitting upright and standing. He had several episodes of sliding off the toilet without any trauma or injuries experienced during these episodes.

On the day of admission he was found unresponsive in his bed. He responded only slightly to sternal rub. Upon arrival at the outside hospital, he was somnolent and answering questions with mumbles and garbled speech. Upon arrival at our hospital, he was more alert and able to answer questions. Staff from the care facility reported that he had been seen at the outside hospital a month ago for similar gait disturbances and decreased mentation.

His psychiatrist decreased his Clozaril dose from 350mg at bedtime to 250mg at his last presentation due to possible interactions with valproic acid and congentin. S.M's other pertinent medications include: bupropion, cabergoline, clozapine, fluoxetine, and trazodone. The patient has a history of heavy drinking for three to four years in the past, but has not drank alcohol since residing at his care facility. He smokes occasionally, but denies recreational drug use.

Review of Systems: S.M. denies any pain, headache, fever, chills, shortness of breath, cough, chest pain, abdominal pain, nausea, vomiting, diarrhea, constipation, dysuria, hematuria, hemoptysis, hematochezia. He denies recent travel, tick bites, and mosquito bites.

Physical Findings: On physical exam, he was alert and oriented and in no acute distress. Musculoskeletal and neurologic exams were significant for normal range of motion and 5/5 strength in bilateral upper and lower extremities. There were no focal neurologic deficits noted and cranial nerves II-XII were grossly intact, including normal extraocular movements. Examination of the neck did not reveal any signs of nuchal rigidity. However, he had an unsteady gait and felt unbalanced when standing. Cardiovascular exam revealed a 2/6 systolic ejection murmur, but was otherwise negative. Respiratory, skin, and abdominal exams were within normal limits.

Differential Diagnosis, Diagnostic Work Up, Hospital Course

Initial work up at the outside hospital included a chest x-ray that was negative for acute findings, negative blood cultures,, EKG revealing normal sinus rhythm, and a negative head CT. Urinalysis was positive for leukocytes and nitrites. Repeat UA was negative for nitrites, positive for a small amount of leukocytes, and positive for trace ketones. Differential diagnosis at this point included urinary tract infection, medication interactions or toxicity, dehydration and electrolyte abnormalities, and recurrent pituitary adenoma or other CNS pathology.

Labs on admission included a CBC that showed an elevated WBC count at 13.6, slightly decreased sodium at 133, and decreased potassium at 3.4. He had a slight normocytic anemia with a Hgb of 12.3 and Hct of 37.8. Albumin was low at 3.4. Together with ketones found in the urine, this may have indicated some insufficient nutrition. Prolactin and valproic acid levels were ordered and found to be within normal limits, ruling down recurrent pituitary adenoma and valproic acid toxicity. Urine and blood cultures were also ordered. Urine cultures were positive for pan-sensitive Enterococcus, confirming suspected UTI.

S.M. received fluid resuscitation, potassium replacement, and appropriate antibiotic therapy for his UTI. His WBC count appropriately trended downwards with antibiotic therapy. The patient's hyponatremia proved to be difficult to correct throughout the course of his hospital stay. Intravenous normal saline was stopped and started several times. His Clozaril dose was decreased further to 200mg at bedtime, with no improvement in symptoms.

He continued to be difficult to arouse in the mornings on hospital days 1-7. He was minimally responsive and answered a few questions with a mumbled voice. He would improve throughout the day, but continued to be unmotivated with a flat affect. However, this was consistent with his baseline according to his care facility staff. He remained unsteady on his feet, according to the

nurses that worked with him in the hospital. With no improvement in symptoms, an MRI of the brain and spine were ordered on hospital day three with no acute findings.

Neurology was consulted on hospital day four and found him to be alert and oriented with good registration, being able to repeat three objects. They noted normal sensation to soft touch, pinprick, and vibration throughout. Romberg sign was negative. Reflexes were brisk aside from the Achilles reflex, which was hypoactive. Upgoing Babinski was noted bilaterally, but without fanning of the toes. The patient exhibited an intention and postural tremor in both upper extremities, with the right being worse than the left. He also had tremulousness in his legs when trying to hold them in position. Gait was limited by this tremulousness. The tremor was attributed to multiple medications, including clozapine and Depakote. The primary team increased the patient's benztropine dose in an effort to improve the tremor.

An EEG was ordered by neurology that revealed evidence of encephalopathy with generalized slow activity and a slow posterior dominant rhythm, but no evidence of seizure activity. A metabolic encephalopathy was suspected and the neurology team suggested measuring levels of thiamine, B6, B12, folate, TSH, and copper. HIV tests to rule out HIV encephalopathy, ammonia levels to rule out hepatic encephalopathy despite negative history of liver disease, and lead levels were also ordered by the primary team. Pending results of several of these tests that would explain the patient's encephalopathy and without any improvement in symptoms, the patient underwent a lumbar puncture on hospital day seven to rule out meningitis or encephalitis. The results were negative for infection.

Vitamin B12, folate, TSH, copper, lead, ammonia, and HIV tests returned within normal limits. However, the result for the patient's thiamine (B1) level returned on hospital day seven and was found to be low at 6nmol/L, with normal being 8-30nmol/L. The patient subsequently received thiamine replacement with 100mg IV thiamine. When the patient was seen the next morning (hospital day eight), he was still difficult to arouse from sleep, but had improved mentation later in the day when compared to previous days. Thiamine was administered again, and the next morning (hospital day nine) he was found sitting in his chair eating breakfast and listening to music. He was very conversational and alert. He stated that he was feeling much better with improvement in his weakness and was requesting to be discharged and returned to his care facility. Tremor was also noted to be improved. Before he was discharged, B6 was also found to be low at 4.3nmol/L, with the normal range being 20-125nmol/L. S.M. was ultimately diagnosed with nutritional deficiencies of thiamine (B1) and pyridoxine (B6). It was believed that thiamine deficiency was the major player in the development of the patient's symptoms, given the dramatic improvement after the administration of thiamine.

Final Diagnosis and Management Plan

Clinically, thiamine deficiency can have several different presentations. Wet beriberi is not likely in this patient because he did not exhibit cardiovascular symptoms. Dry beriberi or Wernicke's encephalopathy would be more likely. According to Caine criteria for diagnosis of Wernicke's encephalopathy, which is more sensitive than the classic triad, a patient can be diagnosed if two out of four of the following are present: eye signs, cerebellar signs, mild memory impairment or confusion, and signs of malnutrition.[2] S.M. had clear evidence of altered mental status, cerebellar

signs with ataxia leading to gait disturbances, as well as evidence of malnutrition with hypoalbuminemia and ketonuria. The patient was also demonstrated to have decreased levels of thiamine in his blood, further supporting this diagnosis. Finally, all other work up that was performed during the patient's hospital stay proved to be negative.

While thiamine deficiency was concluded to be the final diagnosis, this patient presented many diagnostic challenges. There were many confounders that had to be considered in the evaluation of this patient's altered mental status and ataxia. Other diagnoses that were considered throughout the patient's hospital course included medication interactions or toxicity, acute decompensation of mental status due to infection, and acute hyponatremia. These diagnoses are possible explanations for the patient's presentation, as they are all acute processes that were also corrected during the patient's hospital stay. However, the patient improved most rapidly after the administration of thiamine.

After a nine-day hospital stay, the patient was discharged on 100mg PO thiamine daily, with plans to decrease to maintenance dose when symptoms completely resolved. His care facility was also instructed to complete his seven-day course of antibiotics for his urinary tract infection.

 Discussion

According to Isenberg-Grzeda, et al., there are many misconceptions about Wernicke-Korsakoff syndrome, including the misconceptions that it is rare, exclusive to alcoholics, and likely to present with the classic triad for Wernicke's encephalopathy. On the contrary, this condition is likely under diagnosed, occurs in patients with malnutrition secondary to any cause, and rarely presents with the classic triad.[2] This case is a great example to reinforce the inaccuracy of these misconceptions. This case of thiamine deficiency occurred in a patient who was suffering from nutritional deficiencies due to decreased appetite and apathy. He had a remote history of alcohol use but had not had any alcohol for over 10 years. The patient also presented with very vague, non-specific symptoms that did not fulfill the classic triad of Wernicke's encephalopathy. However, this patient did have significant improvement in his symptoms following administration of IV thiamine. This alone is often used diagnostically and reasonably confirms the diagnosis of Thiamine deficiency.[3]

Many expensive and invasive tests were performed in the work up of this patient. If the physicians involved in the care of this patient had considered a higher degree of clinical suspicion for thiamine deficiency and administered IV thiamine, several of these tests may have been avoided. If thiamine replacement had been provided earlier in S.M.'s hospital stay, his symptoms might have resolved before several expensive and invasive tests were ordered, including the MRI of the brain and spine and lumbar puncture.

When a patient presents with any evidence of nutritional deficiency and nonspecific neurologic symptoms or acute heart failure, thiamine deficiency should be on the list of possible diagnoses. Intravenous thiamine should be administered early if there is any suspicion for thiamine deficiency. This may aid in diagnosis if rapid improvement of symptoms occurs, and also prevents the morbidity associated with Wernicke-Korsakoff syndrome in the form of permanent psychosis.[2]

References

1. Russell RM, Suter PM. Chapter 74. Vitamin and Trace Mineral Deficiency and Excess. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson J, Loscalzo J. eds.*Harrison's Principles of Internal Medicine, 18e.* New York, NY: McGraw-Hill; 2012. http://accessmedicine.mhmedical.com.proxy.mul.missouri.edu/content.aspx?bookid=331&Sectionid=40726808. Accessed September 10, 2014.
2. Isenberg-Grzeda E, Kutner HE, Nicolson SE. 2012. Wernicke-Korsakoff-syndrome: under-recognized and under-treated. *Psychocomatics*53: 507-516.http://ew3dm6nd8c.search.serialssolutions.com.proxy.mul.missouri.edu/?sid=Mizzou&genre=article&issn=1545-7206&volume=53&issue=6&date=&year=&pages=507-16&rft_id=info%3Apmid%2F%3E23157990&id=pmid:23157990&atitle=&stitle=Psychosomatics
3. Nguyen-Khoa D. (2014). Beriberi (Thiamine Deficiency).In: Medscape Reference, Khardori R (Ed.), Medscape Reference, New York, NY. Retrieved from http://emedicine.medscape.com/article/116930-overview.

An Interesting Case of Anemia

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Keywords pernicious anemia, vitamin B12 deficiency

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BACKGROUND

Cobalamin (Vitamin B12) deficiency can result in abnormalities in all cell lines which normalize after cobalamin replacement[1]. Moreover, Andres *et al.* reported hematological findings in 201 consecutive patients with vitamin B12 deficiency [2]. Approximately 10% of the patients had life threatening hematological manifestations, including symptomatic pancytopenia (5%), "pseudo"

thrombotic microangiopathy (2.5%), and hemolytic anemia (1.5%). A significant proportion of these patients underwent invasive and comprehensive diagnostic panels to rule out other causes of such abnormalities. At times, these patients were misdiagnosed and treated with aggressive measures such as steroids, polyvalent immunoglobulins, and plasmapheresis[2].

Concurrent hemolysis in patients with Vitamin B12 deficiency has been attributed to intramedullary destruction of red blood cells (ineffective erythropoiesis) [3]. Patients demonstrated complete resolution of hemolysis after vitamin B12 treatments [4]. On the other hand, associations with autoimmune cytopenias have been described previously [5-11], and some features of Pernicious Anemia and these cytopenias can mimic each other. The ineffective erythropoiesis and hemolytic component of cobalamin deficiency can produce increased lactate dehydrogenase activity [12], indirect hyperbilirubinemia [13, 14], a decreased serum haptoglobin level [15], decreased erythrocyte survival [16, 17], and occasionally even methemalbuminemia [15] and hemosiderinuria [18]. Furthermore, a positive direct coomb's test is a common finding in untreated pernicious anemia [19, 22].

CASE PRESENTATION

A 45 year old african american female consulted her primary care physician with a two-week history of progressively worsened generalized fatigue, shortness of breath upon exertion and dizziness. Her dizziness was described as lightheadedness especially when standing up from sitting position. She was found to have hemoglobin of 3.9 mg/dL at the office and was immediately referred to our emergency room for further evaluation and treatment. Her past medical history was positive for diffuse osteoarthritis and iron deficiency anemia. Patient denied hematochezia, hemoptysis or hematuria. She had no history of peptic ulcer disease or over the counter non-steroidal anti-inflammatory drugs (NSAIDS) abuse. However, the patient did report unintentional 40 lbs. weight loss over the past year, ice craving and heavy menstrual periods, which came every 28 days and usually lasted 5 days. Her last menstrual period had started seven days prior and was still present on admission with a heavy flow. The patient was taking only over the counter cold medications.

Her initial physical examination revealed a heart rate of 90 beats per minute, pronounced pallor, no jaundice and 1/6 systolic flow murmur over left sternal border. No palpable abdominal organomegaly. The patient was found to have pancytopenia, with a leukocyte count of 2.36 x 10^3/μL, a hemoglobin level of 5.8 g/dL, and a platelet count of 97×10^3/μL. Her coagulation tests showed an activated partial thromboplastin time (aPTT) of 23.9 seconds and an international normalized ratio (INR) of 1.19. Complete blood count revealed normocytic anemia with a mean corpuscular volume (MCV) of 91.1 fL, and an elevated red cell distribution width (RDW) of 31.9%. Further workup for anemia revealed no evidence of Iron Deficiency Anemia, with an iron level of 61μg/dL, a total iron binding capacity of 290 μg/dL, a ferritin level of 51ng/mL, and a transferrin level of 207mg/dL. A pelvic ultrasound revealed a normal size uterus with a small anterior myometrial fibroid; normal endometrial thickness and normal ovaries.

The peripheral blood smear showed marked schistocytosis, anisocytosis, poikilocytosis, moderate macrocytes, slight polycromasia, hypersegmented polymorphonuclear cells, tear-drop red blood cells and ovalocytes. Myeloid precursors were not present neither did blasts. One

percent of nucleated red blood cells were present. Serum vitamin B12 level was 153 pg/mL (normal 150-800 pg/mL), with a folate level of 413 ng/mL, Homocysteine level of 73.3 μmol/L, and Methylmalonic Acid (MMA) 60.93 of μmol/L. Serum chemistry studies were remarkable for elevated lactate dehydrogenase (LDH) levels at 4632 IU/L, which was significantly out of proportion to the degree of elevation of bilirubin at 2.3 mg/dL; and normal Haptoglobin of 26 mg/dL. She also had normal BUN and creatinine with a slight elevation in transaminases (ALT=40 IU/L, AST=90 IU/L). The corrected Reticulocyte count was 0.53%, showing a lack of a significant bone marrow response to the hemolysis. In addition to this, direct coomb's and fecal occult blood test were negative. Hemoglobin electrophoresis showed normal adult hemoglobin. Further workup revealed normal G6PD (glucose 6 phosphate dehydrogenate) activity, negative Hepatitis B and C serologies, and a positive Hepatitis A IgG indicating prior exposure.

A bone marrow aspiration was performed and cytomorphologic as well as cytogenetic analysis was carried out. Flow Cytometry revealed no detectible evidence for an increased blast population (about 2%). CD56 was aberrantly co-expressed in a subset of the maturing myeloid population. This finding is aberrant and nonspecific, can be associated with myelodysplasia. No evidence for lymphoproliferative disorder was seen. Cytogenetic revealed normal female karyotype without evidence of a chromosomal abnormality. The pathology diagnosis reported was hypercellular marrow with megaloblastic changes. The LDH isoenzymes pattern was non-specific.

During the course of the one-week hospitalization, the patient was transfused with 2 units of packed RBC and started on treatment with intramuscular injections of cobalamin and oral supplementation of folic acid. Further laboratory examinations showed a positive anti-intrinsic factor antibody. An improvement of the pancytopenia, reduction of LDH levels and normalization of bilirubin and transaminases levels were achieved before discharge. Patient was continued vitamin B12 and folate therapy in an outpatient setting.

DISCUSSION

Concurrent hemolysis in patients with vitamin B12 deficiency can result in severe anemia. While its mechanism is not entirely understood, it is believed that the hemolysis results from intramedullary destruction[3.] Our patient presented with irregular menstrual periods and anemia with elevated RDW, but her normal iron indices and normal endometrial thickness, excluded the diagnosis of iron deficiency anemia; and, she had ongoing hemolysis as evidenced by the presence of schistocytes in the peripheral blood smear, high level of LDH and low level of haptoglobin.

The low Reticulocyte count indicated an inadequate bone marrow response to the anemia. However, the hypercellular bone marrow with megaloblastic changes and the peripheral smear with hypersegmented neutrophils indicated folic acid or vitamin B12 Deficiency. The patient's low normal level of vitamin B12 with high MMA levels and a positive anti-intrinsic factor antibody, demonstrated she had vitamin B12 Deficiency (pernicious anemia), resulting in severe intramedullary hemolysis and ineffective erythropoiesis.

Although vitamin B12 Deficiency normally presents with high MCV, in this case, the normal MCV could be explained by average size of macrocytes and schistocytes. Also the thrombocytopenia occurs often as part of the megaloblastic abnormality in severe cobalamin deficiency. It is not due to immune mechanisms, and the platelet count becomes normal with simple vitamin replacement[23], as happened in this case.

Vitamin B12 Deficiency and pernicious anemia can be suspected as they can produce, because of ineffective erythropoiesis, increased LDH activity, indirect hyperbilirubinemia, a decreased serum haptoglobin level, decreased erythrocyte survival, and occasionally even methemalbuminemia and hemosiderinuria. Thus, careful attention should be paid to the possibility of vitamin B12 Deficiency in patients with severe anemia and hemolysis.
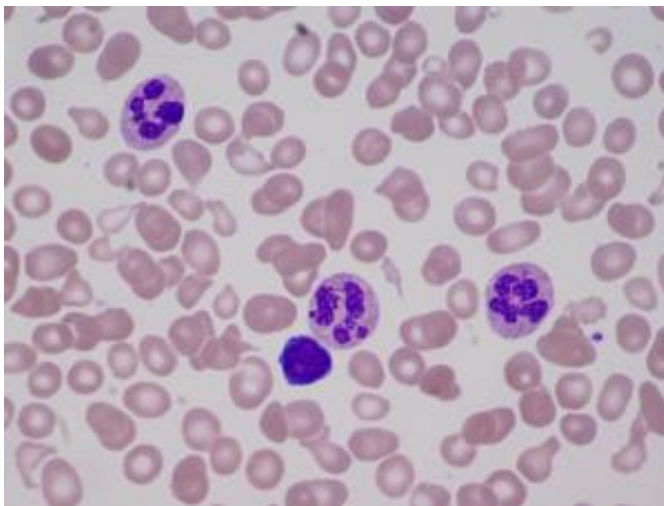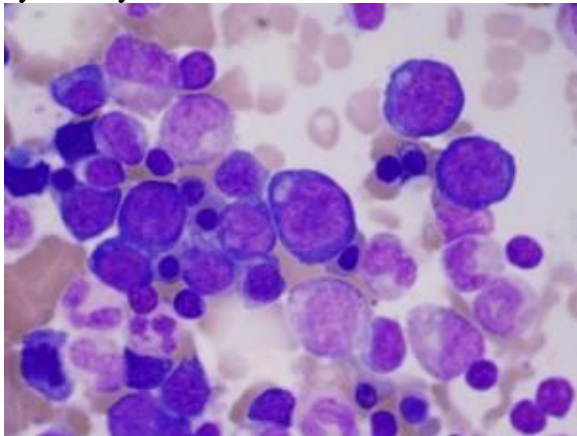
FIGURES

Figure 1. Peripheral smear showing schistocytosis, anisocytosis, and poikilocytosis with hypersegmented neutrophils.

Figure 2. Bone Marrow Aspiration showing Hypercellularity with megaloblastic changes. Flow cytometry showed no evidence of increase blast cells.

REFERENCES

1. Rabinowitz AP, Sacks Y, Carmel R. *Autoimmune cytopenias in pernicious anemia: a report of four cases and review of the literature.* Eur J Haematol. 1990 Jan; 44(1):18-23.
2. Andres E, Affenberger S, Zimmer J, Vinzio S, Grosu D, Pistol G, Maloisel F, Weitten T, Kaltenbach G, Blickle JF: *Current hematological findings in cobalamin deficiency: A study of 201 consecutive patients with documented cobalamin deficiency.* Clin Lab Haem 2006, 28:50-56.
3. Antony AC: **Megaloblastic anemias.** In *Hematology, Basic Principles and Practice.* 4th edition. Philadelphia, PA: Elsevier, Inc; 2005:519-556.
4. Acharya U, Gau JT, Horvath W, Ventura P, Hsueh CT, Carlsen W. *Hemolysis and hyperhomocysteinemia caused by cobalamin deficiency: three case reports and review of the literature.* J Hematol Oncol. 2008 Dec 18; 1:26.
5. Rubio F, Burgin L. *Hemolytic disease complicated by pernicious anemia.* Bull Tufts N Engl Med Ctr 1957: 3: 77-85.
6. Edlen A. *TvP fall av anemia perniciosa med fdrvarvad hamolytisk anemi.* Svenska Lak 1963: 60: 1933-6.
7. Charache P, Hodkinson Ba, Lambiotte B, Mcintyre Pa. *Genetic and auto-immune features of pernicious anemia. 11. Effect of transplacental transfer of antibody to intrinsic factor.* Johns Hopkins Med J 1968: 122: 184-91.
8. Salvidio E, Venzano C, Boccaccio P, Intra E, Ravazzolo R, Gaetani Gf, Ajmar F. *Pernicious anemia followed by autoimmune haemolytic anaemia.* Proc Roy Soc Med 1975: 68: 421-2.
9. Albahary C, Martin S, Sourisseau A. *Maladie de Biermer et Purpura thrombocytopenique chronique autoimmune: une association exceptionnelle.* Nouv Presse Med 1980: 9: 1034.
10. Zittoun R, Zittoun J, Arrago J P, Vigeral P, Cadiou M. *Maladie de Biermer sans anemie, ni megaloblastose.* Ann Med Intern 1983: 134: 569-72.
11. Nel A E. *Primary acquired hypogammaglobulinaemia complicated by antibody-mediated haemolysis and pernicious anaemia.* S Afr Med J 1983: 64: 326-8.
12. Chanarin I. *The Megaloblastic Anaemias.* Oxford: Blackwell Scientific Publications; 1969: 432.
13. Schilling R F, Harris J W. *Liver function in untreated Addisonian pernicious anemia.* J Lab Clin Med 1952: 40: 718-25.
14. Carmel R, Wonge T, Weiner JM, Johnson CS. *Racial differences in serum total bilirubin and in disease (pernicious anemia).* JAMA 1985: 253: 3416-8.
15. Nyman M. *Haptoglobin in pernicious anemia.* Scan J Clin Lab Invest 1957: 9: 168-9.
16. McCarthy CF, Fraser ID, Read HE. *Plasma lactate dehydrogenase in megaloblastic anemia.* J Clin Pathol 1966: 19: 51.
17. Chanarin I. *The Megaloblastic Anaemias.* Oxford: Blackwell Scientific Publications; 1969: 416.
18. Hamilton H E, Degowin E L, Shelts R F, Janney C D, Ellis JA. *Studies with inagglutinable erythrocyte counts. VI. Accelerated destruction of normal adult*

erythrocytes in pernicious anemia; contribution of hemolysis to the oligocythemia. J Clin Invest 1954: 33: 191-205.

19. Carmel R . *Gastric juice in congenital pernicious anemia contains no immunoreactive intrinsic factor molecule: study of three kindreds with variable ages at presentation, including a patient first diagnosed in adulthood.* Am J Hum Genet 1983: 35: 67-77.
20. Selwyn JG , Alexander SS . *A positive Coombs reaction in pernicious anaemia.* Br Med J 1951: 1: 564-5.
21. Forshaw J, Harwood L. *The direct antiglobulin (Coombs) test in megaloblastic anaemia.* J Clin Pathol 1965: 18
22. Pirofsky B, Vaughn M. *Addisonian pernicious anemia with positive antiglobulin tests: A multiple autoimmune disease syndrome.* Am J Clin Pathol 1968: 50: 459-66.
23. Smith MD, Smith DA, Fletcher M. *Haemorrhage associated with thrombocytopenia in megaloblastic anemia.* BR Med J. 1962: 1:982-985.

Hypermucoviscous Klebsiella Pneumoniae Liver Abscess in a Previously Healthy Burmese Male

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Introduction

Discovered over 100 years ago, Klebsiella pneumoniae is a gram-negative pathogen found in the environment and on mammalian mucosal surfaces1. In the Western world, K. pneumoniae most commonly infects the lungs and urinary tract. The majority of these infections occurs in hospitals and long-term care facilities2. However, over the past 20 years, considerable attention has been focused on community-acquired pyogenic liver abscesses (CA-PLA) caused by a hypervirulent variant of K. pneumoniae with a tendency for metastatic spread2,3. Most of these cases have

been reported from Taiwan, where this organism is the leading cause of PLA. Since the mid-1980s, over 900 patients with PLA due to K. pneumoniae were reported from East and Southeast Asian countries. Nonetheless, K. pneumoniae CA-PLA is becoming a global issue as evidenced by confirmed cases in North America and Europe with the majority of hosts being of Asian descent. A total of fifteen cases of hypermucoviscous K. pneumoniae CA-PLA have been reported in the United States4-9. Purported theories for the stratified prevalence of K. pneumoniae pyogenic liver abscesses include genetic susceptibility, socioeconomic factors, and interaction between bacterial and host variables2. The hypermucoviscous strain of K. pneumoniae is an emerging phenotype with very critical distinguishing features. These include a community-acquired origin, absence of underlying hepatobiliary disease in the host, and invasive complications, such as meningitis, brain abscess, endophthalmitis, endovascular infections, and colon cancer. This report details the first reported case of hypermucoviscous K. pneumoniae CA-PLA in the state of Missouri identified in an otherwise healthy individual of Asian descent.

Case Presentation

A 38 year-old Asian male with no previous medical diagnoses presented to the emergency department (ED) with right upper quadrant abdominal pain, headache, and myalgia. He denied recent abdominal surgery, biliary disease, diabetes mellitus, recent travel, or sick contacts. The patient was examined in the ED and discharged home with a diagnosis of viral syndrome.

However, the patient's symptoms became more severe and he returned to the ED three days later reporting fevers up to 102.5°F, a severe left-sided tension-type headache, pleuritic chest pain, dyspnea, and anorexia.

The patient was born and raised in Burma and moved to Malaysia later in life. He emigrated from Malaysia to the United States 5 years ago and had not left the United States since then. He had no history of significant childhood illnesses. He reported recent contact with visitors from Thailand, who were all healthy at the time of interaction.

Significant findings on physical examination included extreme tenderness to palpation of the right upper quadrant. Laboratory studies were remarkable for leukocytosis (WBC 12,100/mm3 with 73.4% granulocytes and 11.9% monocytes), hyperbilirubinemia (1.4 mg/dL), mild transaminitis (ALT 63 U/L, ALP 166 U/L), and evidence of inflammation with an ESR of 57 mm/hr and CRP of 9.1 mg/dL. Urinalysis was notable for amber colored urine, presence of bilirubin, 2.0 Ehrlich U/dL urobilinogen, 20-30 RBCs/hpf, 30mg/dL protein, and 15 mg/dL ketones.

A CT of the abdomen and pelvis with intravenous contrast revealed a peripherally enhancing hypodense mass in hepatic segment IVa with no significant central enhancement on delayed phase imaging. Approximately 20 mL of purulent fluid was removed from the abscess via IR-guided biopsy and drainage. An abscess drainage catheter was not introduced secondary to the high puncture with possibility of pleural reflection transgression.

The patient was started on IV ceftriaxone and metronidazole, diagnostic testing was ordered, and an abscess gram stain and anaerobic culture was performed to identify the culprit pathogen.

Results of diagnostic laboratory testing are as follows:

HIV 1,2 Antigen Antibody: Nonreactive
Cryptosporidium: Negative
Giardia Antigen by EIA: Negative
Stool ova and parasites :Negative
Quantiferon-TB Gold: Negative
Abscess culture – anaerobic Hypermucoviscous K. pneumonia

Culture plate demonstrating the hypermucoviscous characteristics of the isolate. Strains of Klebsiella with the hypermucoviscosity phenotype are identified with the string test. A colony is lifted off the growing medium with an inoculation loop. A string greater than 5 mm is considered a positive result.

On follow-up ultrasound of the right upper quadrant the following day, the liver abscess had not significantly changed in size compared with the initial CT scan. However, no new fluid collection or perihepatic free fluid was visualized and the patient's headache and abdominal pain had improved. Another 20mL of purulent fluid was drained from the abscess and a silicon drain was placed.

The patient was discharged on hospital day 7 on a six-week course of oral ciprofloxacin. Five days after discharge he presented to the clinic for follow up with his silicon drain in place. Symptomatically the patient seemed to be improving. However, since discharge, the patient was continuing to drain approximately 20 mL of fluid each day. A colonoscopy was scheduled in one month to screen for colorectal malignancy.

Discussion

This previously healthy 38 year-old patient initially presented to the hospital with symptoms consistent with a viral illness. However, worsening abdominal pain and fevers led to further workup and identification of a hepatic abscess of the right lobe. The patient's history of inhabitance in Malaysia five years prior and an otherwise unremarkable past medical and social history increased suspicion for a primary pyogenic liver abscess caused by K. pneumoniae. Clinical features of pyogenic liver abscess include fever, chills, right upper quadrant tenderness, abdominal pain, leukocytosis, elevated ALT and AST, elevated ALP, and hyperbilirubinemia12.

In the United States, pyogenic liver abscesses are most often polymicrobial with streptococci and Escherichia coli being the most common pathogens1. However, monomicrobial liver abscesses caused by Klebsiella pneumoniae infection have become more prominent in recent years 10. K. pneumoniae infection occurs most commonly in individuals with a compromised immune response, such as diabetes, malignancy, and alcoholism. It is also more common in patients with hepatobiliary disease, colorectal disease or a history of intraabdominal disease or trauma. K. pneumoniae can also occur in the absence of hepatobiliary disease11.

The prevalence of hypermucoviscous K. pneumoniae CA-PLA in individuals of Asian descent is not well understood. It is hypothesized that an undetermined host genetic factor may predispose these individuals to intestinal colonization by more virulent strains of K. pneumoniae. It is posited that liver abscess may occur when this more virulent strain of bacteria translocates across the intestinal epithelium to the liver13. Interestingly, individuals colonized with this more virulent strain of K. pneumoniae do not always develop infection2. However, the associated risk factors, mechanisms of infection, and outcomes of K. pneumonia liver abscesses remain largely unclear.

Studies have shown that the mucoviscosity-associated gene A (magA) and regulator of the mucoid phenotype A (rmpA) are the main contributors to the increased virulence of the hypermucoviscosity phenotype of K. pneumoniae that causes CA-PLA in Taiwan13,14. Specifically, magA+ K. pneumoniae strains demonstrate increased serum resistance, greater resistance to phagocytosis, and greater lethality in mice14. RmpA is a regulatory gene for the synthesis of the extracapsular polysaccharide and positively controls the mucoid phenotype of K. pneumoniae. Overproduction of polysaccharide is responsible for the mucoid phenotype of K. pneumoniae. The bacterial chromosome encodes the rmpA gene, but the mucoid phenotype itself is regulated by rmpA located in a plasmid13. In addition, this strain of K. pneumoniae can more efficiently acquire iron for the purposes of growth and replication. Overall, both rmpA and magA genes are essential for the induction of the hypermucoviscosity phenotype by K. pneumoniae.

Thus far, only 15 cases of K. pneumoniae strains with the hypermucoviscosity phenotype have been reported in cases of CA-PLA in the United States5-9. Despite the small number of reports, the incidence of this disease is rising. Furthermore, more than one-third of individuals infected with hypermucoviscous strains of K. pneumoniae are more likely to develop complications, such as meningitis, endocarditis, subcutaneous muscular abscesses, osteomyelitis, pulmonary emboli, pleural empyema or endophthalmitis as compared than individuals infected with hypermucoviscous-negative strains2. Even more concerning is the finding that these serious, life-threatening complications can develop in young, previously healthy individuals15. The current mortality rate for hypermucoviscous K. pneumoniae infection ranges from 3-42%2. Currently, this hypervirulent strain of K. pneumoniae remains uniformly resistant to ampicillin, but is susceptible to most antibiotics, including third and fourth-generation cephalosporins, monobactam, carbapenems, and ciprofloxacin2. However, it is possible that as the disease becomes more prominent, this stain will become resistant to antimicrobials leaving few options for treatment other than supportive care2,13,15.

Conclusion

We report the case of a 38 year-old previously healthy Burmese man who presented with abdominal pain, headache, myalgia, and back pain. He was found to have leukocytosis, transaminitis, hyperbilirubinemia, and evidence of systemic inflammation. A hypodense hepatic mass was identified with a CT of the abdomen. The patient was ultimately diagnosed with hypermucoviscous K. pneumoniae CA-PLA.

This case provides additional evidence for the emergence of hypermucoviscous K. pneumoniae CA-PLA outside of East Asia and supports the need for continued research to gain a better understanding of its pathogenesis predilection for individuals of Asian decent. This report also delineates the importance of acknowledging the dynamic state of infectious disease, the shifting racial demographics in the Western world, and the ever-present potential for antibiotic resistance. With this information clinicians will be more equipped to identify and treat a potentially fatal disease in individuals with symptoms of a seemingly self-limiting infection.

References
1. Siu K, Kuo-Ming Y, Jung-Chung L, Chang-Phone F, Feng-Yee C. Klebsiella pneumoniae liver abscess: a new invasive syndrome. Lancet Infect Dis 2012;12:881-887.
2. Shon A, Rajinder B, Russo T. Hypervirulent (hypermucoviscous) Klebsiella pneumonia: A new and dangerous breed. Virulence;4:107-118.
3. Keynan T, Karlowsky J, Wali T, Rubinstein E. Pyogenic liver abscess caused by hypermucoviscous Klebsielle pneumoniae. Scan J Infect Dis 2007;39:828-830.
4. Ali A, Smalligan R, Ahmed M, Khasawneh F. Pyogenic liver abscess and the emergence of Klebsiella as an etiology: a retrospective study. Int J Gen Med 2014;7:37–42.
5. Fierer J, Walls L, Chu P. Recurring Klebsiella pneumoniae pyogenic liver abscesses in a resident of San Diego, California, due to a K1 strain carrying the virulence plasmid. J Clin Microbiol 2011; 49:4371- 3; PMID:21998428; http://dx.doi.org/10.1128/ JCM.05658-11.
6. Pastagia M, Arumugam V. Klebsiella pneumoniae liver abscesses in a public hospital in Queens, New York. Travel Med Infect Dis 2008; 6:228-33.
7. Nadasy K, Domiati-Saad R, Tribble MA. Invasive Klebsiella pneumoniae syndrome in North America. Clin Infect Dis 2007; 45:e25-8.
8. Frazee BW, Hansen S, Lambert L. Invasive infection with hypermucoviscous Klebsiella pneumoniae: multiple cases presenting to a single emergency department in the United States. Ann Emerg Med 2009; 53:639- 42.
9. Pope J, Teich D, Clardy P, McGillicuddy D. Klebsiella pneumonia liver abscess: an emerging problem in North America. Journ Emer Med 2008;41;5;103-105.
10. Lederman E, Crum N. Pyogenic liver abscess with a focus on Klebsiella pneumoniae as a primary pathogen: an emerging disease with unique clinical characteristics. Amer Jour Gastroenterology 2005;322-330.
11. McCabe R, Lambert L, Freeze B. Invasive Klebsiella pneumonia infections, California, USA. Emer Infect Diseases 2010; 16; 1490-1491.
12. Nazir N, Penfield J, Hajjar V. Pyogenic liver abscess. Cleveland Clinic J Med 2010;77:436-427.
13. Li W, Sun G, Yu Y, Li N, Chen M, Jin R, Jiao Y, Wu H. Increasing Occurrence of Antimicrobial-Resistant Hypervirulent (Hypermucoviscous) Klebsiella pneumoniae Isolates in China 2014; 58:225-232.
14. Fang FC, Sandler N, Libby SJ. Liver abscess caused by magA+ Klebsiella pneumoniae in

North America. J Clin Microbiol 2005; 43: 991–2.
15. Lee H, Chuang Y, Yu W, Lee N, Chang C, Ko N, Wang L, Ko W. Clinical implications of hypermucoviscosity phenotype in Klebsiella pneumoniae isolates: association with invasive syndrome in patients with community-acquired bacteremia. J Int Med; 259:606-614.

Denosumab-Induced Severe Hypocalcemia in a Patient with Crohn's Disease.

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 Introduction

Osteoporosis occurs with increased prevalence in individuals with inflammatory bowel disease (IBD), and as such, these patients are at risk for osteoporosis-related fractures.   Although bisphosphonates remain the most commonly used class of drugs for managing osteoporosis, the effectiveness of oral bisphosphonates in patients with IBD may be diminished due to distressing gastrointestinal side effects, which hinder compliance, and also due to poor absorption by diseased intestine.

While intravenous bisphosphonate therapy remains an option for these patients, denosumab has emerged in recent years as an alternative bone-modifying agent. Denosumab received FDA approval for treatment of postmenopausal osteoporosis in 2010 and clinical trials have demonstrated that this medication is both efficacious and well tolerated. Hypocalcemia is a known adverse effect of this medication, although in clinical trials, denosumab has been well tolerated, and numerous trials, most notably the FREEDOM trial (and its two-year extension trial), have failed to demonstrate a significant risk of hypocalcemia while receiving denosumab [1]. However, there have been no formal studies assessing for the risk of hypocalcemia while receiving denosumab in patients who have gastrointestinal disorders such as IBD. This report details a patient with a history of corticosteroid-treated Crohn's disease, who developed severe, symptomatic hypocalcemia shortly after beginning denosumab therapy.

Case Presentation

A 64-year-old Caucasian woman presented to the emergency department with a two-week history stiffening of her hands and face, myalgias, weakness, and edema of the hands and feet. Additionally, on the day of presentation, she developed garbled speech. The patient had a past medical history significant for Crohn's disease, for which she was status-post ileocolectomy with only six feet of remaining intestine; osteoporosis; gouty arthritis; breast carcinoma with left mastectomy in 2006; renal carcinoma with ablation in 2009; and lymphoma. 72 hours prior to initial onset of symptoms, the patient was started on denosumab to treat her osteoporosis. Of note, the patient was taking prednisone 10 mg per day for the past year to manage her Crohn's disease.

Physical exam in the emergency department was remarkable for positive Chvostek and Trousseau signs, and patient was alert but unable to speak, due to mandibular tetany. Blood testing revealed hypocalcemia with serum calcium of 3.9 mg/dL. Other notable laboratory findings included a PTH of 5,679 pg/mL (normal 15-65 pg/mL), a 25-hydroxy vitamin D of 9 ng/mL (normal 30-80 ng/mL), a creatinine of 1.4 mg/dL, and an alkaline phosphatase of 205 IU/L. She was admitted to the medical intensive care unit and placed on telemetry due to concerns that the patient might develop hypocalcemia-induced prolonged QT interval. Throughout the patient's three-day hospital stay, she received a total of 28 grams of IV calcium gluconate. Additionally, she was started on calcitriol 0.25 mg/day and oral calcium (350 mg) and vitamin D (200 IU) 3 tablets, three times per day. At the time of discharge, the patient's signs and symptoms of hypocalcemia had resolved, although her calcium level remained relatively low at 6.6 mg/dL. Of note, baseline calcium and vitamin D levels were not obtained prior to starting the patient on denosumab.

Discussion

Inflammation-Induced Osteoporosis

Osteoporosis is thought to be present in up to 70% of patients with IBD, depending on the population, due to a number of factors including inflammation, malabsorption (due to disease activity and/or extensive intestinal resection), generalized poor nutritional status, and glucocorticoid use[2,3]. Inflammation in IBD leads to bone density loss, as over-activation of T cells and the resulting cytokine release stimulates the receptor activator of nuclear factor KB ligand (RANKL). RANKL, in turn, binds to RANK receptors on osteoclasts, promoting osteoclastic activity, and thus bone resorption. In understanding this physiology, it could be reasoned that denosumab may be the ideal bone-modifying agent for these patients. Denosumab, a human monoclonal antibody, acts by binding to and inhibiting RANKL. This inhibitory action effectively counteracts the cytokine release by proinflammatory cells as it prevents osteoclast formation, decreases bone resorption and increases bone mass.

Role of Malabsorption

However, as mentioned above, this inflammatory-induced cytokine cascade is only one mechanism of several that are thought to contribute to the development of osteoporosis in these

patients. Another major contributing factor is from bone loss secondary to nutrient malabsorption. Patients with Crohn's disease, in whom the small intestine is involved—specifically patients with inflammation, chronic fibrosis or who are status post removal of the terminal ileum—may have decreased absorption of vitamin D, and thus decreased calcium levels, due to impaired bile salt reabsorption [2]. Poor vitamin D and calcium absorption leads to the development of secondary hyperparathyroidism, which in turn increases bone loss as a result of increased resorption. A multitude of studies exploring the prevalence of vitamin D deficiency in patients with Crohn's disease have yielded variable results, with a range of 27-68%[4]. For example, a 2011 prospective study sought to assess for Vitamin D deficiency in 81 patients with Crohn's disease, and found that 63% of studied patients had subnormal levels[5]. Interestingly, of these 63% of patients with low levels of vitamin D, 43% were actively taking a vitamin-D containing supplement. Of note, most patients who were taking a supplement were taking a multivitamin containing a relatively low dose of vitamin D (200-400 IU) [5]. This finding suggests that providers may need a more aggressive approach for vitamin D (and calcium) supplementation in patients who are at risk for deficiency due to comorbid conditions (malabsorptive diseases, chronic kidney disease). Osteoporosis secondary to vitamin D deficiency cannot be corrected with denosumab or other bone-modifying agents.

Glucocorticoid-Induced Osteoporosis

Glucocorticoids further contribute to osteoporosis in a number of ways. They stimulate osteoclasts by increasing RANKL levels, while increasing osteoblast apoptosis and decreasing osteoblast function and life span. Glucocorticoids also stimulate osteocyte apoptosis. Furthermore, they inhibit calcium absorption from the gastrointestinal tract and induce renal calcium loss[6,7]. The role of denosumab in treating patients with IBD who are receiving glucocorticoid therapy is less clear. While this medication can correct glucocorticoid-induced osteoclast stimulation, osteoclast activity appears to play a smaller role in the pathogenesis of glucocorticoid-induced osteoporosis than it does in the pathogenesis of other types. There are additional concerns that concurrent use of glucocorticoids and denosumab may increase a patient's infection risk[6,7].

Hypocalcemic Effect of Denosumab

While denosumab seems promising for treating osteoporosis in patients with IBD, osteoclast inhibition raises concerns for hypocalcemia, as the body has lost its means for harvesting additional calcium when blood levels drop. Fortunately, this complication is rare; current estimates of hypocalcemia incidence while taking denosumab are 1.7%[8,9]. Despite this apparently low occurrence, the FDA label does caution about the potential for patients to develop hypocalcemia due to post-marketing reports of severe, symptomatic hypocalcemia with denosumab use. Not surprisingly, patients with chronic kidney disease and malabsorption syndromes are most at risk for developing this complication[1]. Importantly, denosumab has not been formally studied in patients with gastrointestinal disorders. The FREEDOM study, which is perhaps the most well-known clinical trial for assessing denosumab efficacy and safety, failed to uncover an increased risk of hypocalcemia in its study patients, but also excluded patients with any conditions that could affect bone metabolism (malabsorptive disorders, kidney disease) from participating in the study[10]. As such, the results of this study should not be generalized to this

population of patients. Patients with these conditions are clearly more likely to develop severe hypocalcemia while undergoing denosumab treatment because many have hypocalcemia at baseline.

In 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) released a report warning of the possible risk of severe symptomatic hypocalcemia. Although the greater concern for hypocalcemia occurs with the 120 mg dose (Xgeva) which is used for prevention of skeletal related events in patients with bone metastases, symptomatic hypocalcemia has also been reported in patients receiving the 60 mg dose (prolia). Based on these reported hypocalcemic events, the MHRA cautioned healthcare professionals to avoid use of denosumab 60 mg (for osteoporosis indications) in patients with any degree of hypocalcemia. The MHRA also reiterated the importance of adequately supplementing calcium and vitamin D in patients receiving this medication, and vigilantly following blood levels of these nutrients in patients[11].

Learning Points

- Osteoporosis is prevalent in patients with IBD, particularly Crohn's disease, and its cause is multifactorial.
- Denosumab, a RANKL inactivator, may prove helpful in minimizing osteoporosis induced by the large inflammatory component of IBD and its resulting stimulation of the RANKL-RANK interaction for osteoclast activation. However, concerns for hypocalcemia and a lack of clinical trials studying denosumab' s effects in patients with malabsorptive disorders should limit its use in this patient population at this time.
- Should denosumab be used for patients with malabsorptive disorders, it is imperative that these patients have normal calcium and vitamin D levels prior to beginning treatment, and calcium and vitamin D levels should be monitored frequently throughout duration of treatment. Baseline levels must be obtained.
- More research is needed to identify target calcium and vitamin D levels (and thus appropriate supplementation dosages) for osteoporotic patients with malabsorptive disorders who may benefit from denosumab therapy.

References

1. Diab, Dima L., and Nelson B. Watts. "Denosumab in Osteoporosis." *Expert Opinion on Drug Safety* 13.2 (2014): 247-53.
2. Targownik, Laura E., Charles N. Bernstein, and William D. Leslie. "Inflammatory Bowel Disease and the Risk of Osteoporosis and Fracture." *Maturitas* 76.4 (2013): 315-19.
3. Hogezand, R. A Van, and N. A. T. Hamdy. "Skeletal Morbidity in Inflammatory Bowel Disease." *Scandinavian Journal of Gastroenterology* 41.S243 (2006): 59-64
4. Javorsky, Bradley R., Nelly Maybee, Shetal H. Padia, and Alan C. Dalkin. "Vitamin D Deficiency in Gastrointestinal Disease." *Practical Gastroenterology* 36th ser. (2006): 52-72

5. Suibhne, Treasa Nic, Gerry Cox, Martin Healy, Colm O'morain, and Maria O'sullivan. "Vitamin D Deficiency in Crohn's Disease: Prevalence, Risk Factors and Supplement Use in an Outpatient Setting." *Journal of Crohn's and Colitis* 6.2 (2012): 182-88.
6. Adler, Robert A. "Glucocorticoid-Induced Osteoporosis: Management Update." *Current Osteoporosis Reports* 8.1 (2010): 10-14.
7. Dore, R. K. "How to Prevent Glucocorticoid-induced Osteoporosis." *Cleveland Clinic Journal of Medicine* 77.8 (2010): 529-36.
8. Katz, Seymour, and Stuart Weinerman. "Osteoporosis and Gastrointestinal Disease." *Gastroenterology and Hepatology* 6.8 (2010): 506-17.
9. Bridgeman, Mary Barna, and Rolee Pathak. "Denosumab for the Reduction of Bone Loss in Postmenopausal Osteoporosis: A Review." *Clinical Therapeutics* 33.11 (2011): 1547-559.
10. Moen, Marit D., and Susan K. Keam. "Denosumab: A Review of Its Use in the Treatment of Postmenopausal Osteoporosis." *Drugs Aging* 28.1 (2011): 63-82.
11. "Denosumab: fatal cases of severe symptomatic hypocalcaemia, and risk of hypocalcaemia at any time during treatment—monitoring recommended." *Drug Safety Update* 6.3 (2012).

Unusual presentation of Coxsackie B Rhabdomyolysis: Case Report and Literature Review

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Introduction: Coxsackie virus infections occur throughout the year, but have an increased in the summer and fall (1). It is often self-limited and resolves with only symptomatic treatment, but the virus has been linked to rhabdomyolysis in case reports. Though the exact mechanism of viral rhabdomyolysis is still unknown, the end result is destruction of myocytes and the release of toxins into the circulation (2, 3). The results of rhabdomyolysis can be limited to myalgia or can be severe enough to require dialysis (2,4). It is therefore important to recognize viral causes

to this diagnosis so as to treat it before the patient has lasting effects. Here, we present the case of an adult male with diffuse myalgia who was diagnosed with rhabdomyolysis with serologically positive Coxsackie B virus.

Case Report: Patient is a 36 year old Caucasian male with PMH of Hepatitis C untreated, seizure disorder, and who presented to the University Hospital ED with complaints of progressively worsening diffuse myalgia with nausea/vomiting, pain with urination, and hematuria x1 week. He came to the ED just a few days earlier with similar complaints and was treated with pain medication for nephrolithiasis per CT that showed a punctate nonobstructing right renal calculus. He described the pain as "being hit by a bat all over," worsened by activity, and slightly relieved with pain medication. The myalgia had originally been intermittent, but had recently become constant. He also reported having black tarry stool x 1 week and dizziness on standing. He had pain in the center of his chest with coughing and vomiting, palpitations for 3-4 days, chills, night sweats and numbness in his feet for 2 days. He denied fevers. He also reported worsening scrotal and penile pain x 1 week with no associated rash or swelling. He had not had a seizure in many years Patient had not taken any medications for many months. . Patient had recently moved to Columbia from the state of California and had been camping, but denied bites from insects or animals.

On admission, the patient had normal vital signs. On physical exam, the patient was obese and in mild distress due to pain. The exam was significant for diffuse tenderness to palpation of the chest, abdomen, penis, and scrotum. Digital rectal exam showed a boggy and tender prostate.

His complete blood count was within normal limits on both admission and during the course of his admission. Complete metabolic panel was within normal limits, but he had a mildly elevated lipase (66 units/L) with a normal amylase (99 unit/L). Urinalysis was significant for greater than 30 RBC/hpf and an elevated specific gravity at greater than 1.030. Urine drug screen was negative except for opiates, which he had been prescribed in the ER a few days ago. Lactic acid, PSA and TSH were normal His CT abdomen showed partial small bowel obstruction/ ileus, sigmoid diverticulosis, right nonobstructing renal calculus, and calcifications within the prostate. Scrotal U/S was significant for nonspecific small bilateral hydroceles and findings suggestive of prior epididymitis.

He remained afebrile for the duration of his inpatient stay. His specific gravity normalized after IV hydration with normal saline. He was started on Levaquin 500mg PO qday x30 days for prostatitis. On hospital day 4, CK was found to be elevated at 857 unit/L and reached a high of 2700 unit/L. CK-MB was within normal limits (4.8ng/mL). Aldolase was elevated at 10.9 unit/L.. The patient was started on IVF, and CK was trended down to 1264 unit/L at discharge. Basic metabolic panels were ordered approximately every other day and all values were within normal limits. He was started on doxycycline 100mg BID for a working diagnosis of tick-borne illness until the return of labs, but the patient had a rash reaction to the drug. Doxycycline was discontinued. During work up of his nonspecific abdominal pain, the patient was found to be negative or within normal limits for all of the following: CMV (IgG and IgM), Lyme disease, Francisella tularensis (IgG and IgM), Leptospira Ab, EBC (IgG and IgM) Erlichia (IgG and IgM), RMSF, HIV, RPR, Gonorrhea and Chlamydia. Patient was positive for elevated titers to Coxsackie virus B 1-5. Urine myoglobin and FOBT were negative. Urine culture had no growth

concerning for UTI, and blood cultures returned with 1 of 2 positive for Micrococcus luteus/lylae, a contaminant. He was discharged home with pain medication, Levaquin, and tamsulosin with diagnoses of prostatitis and Coxsackie virus rhabdomyolysis. He was lost to follow-up with his primary care doctor for rhabdomyolysis and urology for hematuria work-up/prostatitis.

Discussion:

Rhabdomyolysis in adults is commonly due to illicit drug use, alcohol abuse, medical drugs, muscle disease, trauma, seizures, and immobility. However, it can also be caused by infection, as was the case in our patient. Bacterial, fungal, protozoan, and viral myositis can all lead to rhabdomyolysis if severe (1). Though influenza is the most common cause of rhabdomyolysis, it is not the only virus capable of causing muscle damage (5). Enteroviruses, including Coxsackie and ECHO viruses, have been implicated multiple times in case reports along with HIV, Ebstein-Barr virus, cytomegalovirus, and varicella-zoster virus to name a few (1). Our patient tested positive for Coxsackie virus B 1-5, and his few day history of chills and night sweats before presentation to the ER might have been the prodrome of the infection. He also had the appropriate fourfold increase in titer that suggests acute infection (6). Coxsackie virus has been named a culprit in rhabdomyolysis cases in a wide range of ages. Treatment is geared toward symptom control, and patients often fully recover with aggressive intravenous hydration (3, 5). However, serious complications can arise, and clinicians should be wary. There have been documented cases of rhabdomyolysis severe enough to result in compartment syndrome and acute tubular necrosis requiring hemodialysis (2, 4). Rhabdomyolysis can also result in electrolyte abnormalities and cardiac arrhythmias (3). A recognized clinical condition caused by Coxsackie virus B, in addition to rhabdomyolysis, is pleurodynia syndrome (aka- the Devil's grip): this infectious myositis syndrome consists of paroxysmal, sharp, thoracic and upper abdominal pain with tender chostochondral muscles (5, 6). Viral myositis does not often progress to rhabdomyolysis, but clinicians should be alert if the myalgia/myositis persists for an extended amount of time or if the severity increases. Our patient had muscular chest and abdominal pain, but the tenderness expanded to just above his thighs. Our patient may have possibly had a component of pleurodynia syndrome, though it is often found in children. This patient also had prostatitis that further complicated his diagnosis. Though the patient denies history of prostatitis, his prostatic calcifications may be an indication of chronic inflammation. Chronic pelvic pain syndrome has been studied in patients with chronic prostatitis, and abdominal pain/pelvic tenderness was noted in half the patients in one study (7).

Conclusion:

Our patient presented with physical exam and lab findings significant for chest, abdominal, and pelvic tenderness, an elevated CK, positive Coxsackie virus B serology, and prostatitis. Overall, rhabdomyolysis is the most likely cause for the patient's diffuse myalgia, especially when considered in conjunction with his elevated CK, and his prostatitis was an additional, though unrelated, diagnosis. Viral myositis is a known cause of rhabdomyolysis, but it can be easily overlooked in a patient. It is a clinical diagnosis that may not always be confirmed with positive viral serology. The severity of rhabdomyolysis also varies from patient to patient; in some patients, CK values of 250,000 unit/L was enough to cause renal failure, but another case with a

CK of 600,000 unit/L had no renal dysfunction (2, 3). Therefore, viral rhabdomyolysis is a diagnosis that needs to be made early and treated aggressively with intravenous fluids due to its unpredictable nature in causing serious complications.

References:

1. Khan FY. (2009). Rhabdomyolysis: a review of the literature. Neth J Med. Vol 67(9):272-83.
2. Crum-Cianflone NF. (2010). Nonbacterial myositis. Curr Infect Dis Rep Vol 12:374-382.
3. Crum-Cianflone NF. (2008). Bacterial, fungal, parasitic, and viral myositis. Clin Microbiol Rev Vol 21(3): 473-494.
4. Fodili F and van Bommel EFH. (2003). Severe rhabdomyolysis and acute renal failure following recent Coxsackie B virus infection. Neth J Med Vol 61(5):177-179.
5. Marinella M. (1998). Exertional rhabdomyolysis after recent coxsackie B virus infection. South Med J. Vol 91(11):1057-9.
6. Shoskes DA, Berger R, Elmi A, Landis JR, Propert KJ, Zeitlin S. (2008). Chronic Prostatitis Collaborative Research Network Study Group. Muscle tenderness in men with chronic prostatitis/chronic pelvic pain syndrome: the chronic prostatitis cohort study. J Urol. Vol. 179(2):556-60. Epub 2007 Dec 21.
7. Nauss MD, Schmidt EL, Pancioli AM. (2009). Viral myositis leading to rhabdomyolysis: a case report and literature review. Am J Emerg Med. Vol 27(3):372.e5-372.e6.

A Case Series On Fixed Drug Eruptions

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Patient #1: A 60 year old male truck driver with a history of recurrent skin boils presented with painful lesions on the glans penis that started a few days prior. A week ago he was treated with co-trimoxazole for skin abscesses on the left leg. The penile lesions were noted as vesicular eruptions that eventually coalesced and there was absence of discharge, scrotal involvement, or lymphadenopathy. He reported a similar episode one year ago following a course of co-

trimoxazole for skin abscesses. He denied fever, chills, malaise, or oral lesions. He had no drug allergies and was not taking any other drugs. He denied tobacco; illicit drugs, high risk sexual behavior, and rarely had alcohol. On exam, vital signs were stable, edematous and erythematous glans with shallow based tender ulcerations was noted, but otherwise rest of the exam was unremarkable. No other active skin abscesses or lesions. The basic laboratory work-up including blood counts and serum chemistries were normal. HIV Ag/Aby test was non reactive, Nucleic acid amplification test (NAAT) for Gonococci/Chlamydia was negative, RPR was non-reactive, PCR for HSV from the genital lesions was negative, and Hepatitis C Antibody was also negative. Images as below. Infectious diseases team was consulted for suspicion for sexually transmitted diseases and a diagnosis of fixed drug eruptions secondary to co-trimoxazole was made. Dermatology was then consulted and concurred with our diagnosis. Patient was advised not to take this drug ns future.

Patient #1

Patient #2: A 25 year old male with paranoid schizophrenia presented with seizures and painful lesions on the glans penis and scrotum. The patient had a long history of seizures and was recently started on lacosamide a week ago. He had a history of heroin use and had been incarcerated for 8 years. He lived in an assisted living home and reported no sexual activity. He denied fever, chills, malaise, penile discharge or oral lesions. He did not remember any drug allergies and does not take any other medications. His family history was non-contributory. On exam, vital signs were stable, a non-pruritic macular rash on hands, back, and torso was noted, and tender ulcerations with erythematous base were noted on glans penis and scrotum with exudates on the surface (Images Below). The laboratory work-up consisted of a normal blood cell counts and serum chemistries. HIV Ag/Aby was non reactive and Urine NAAT for Gonococci and chlamydia was negative. RPR was non-reactive, HSV-PCR was negative on ulcer swabs and Hepatitis C antibody negative. Infectious diseases consult service arrived at a clinical diagnosis of Fixed drug eruptions from lacosamide. Dermatology was consulted and they concurred with this clinical diagnosis. An alternative antiepileptic was chosen by the primary neurology team.

Patient #2

Discussion:

Fixed drug eruptions typically present as one or more annular erythematous or necrotic lesions, ulcers or patches (0.5-5 cm) as a result of a systemic exposure to a drug. The lesions may last days to weeks and often resolve with residual hyperpigmentation after stopping the offending drug. The most common sites of occurrence include the lip, genitalia, hip, low back/sacrum, or proximal extremity. The lesions may develop any time to two weeks from the initial drug exposure. Fixed drug reactions make up 16-21% of all cutaneous drug eruptions with a male to female ratio of 1:1.1 at a mean age of 30 years. Other common symptoms are pruritus, burning pain and rash. It can rarely result in fever, nausea, diarrhea, abdominal cramps, anorexia, dysuria, and/or malaise. The most common drug classes implicated are analgesics, muscle relaxants, sedatives, anticonvulsants, and antibiotics. The top five drugs implicated, in particular, are penicillins, tetracyclines, sulfonamides, pyrazolones, and barbiturates. The exact pathophysiology is unknown. Most recent research shows that drug acts as a hapten (drug) and preferentially binds to the basal keratinocyte, that then causes release of TNF-α and ICAM1 and induces CD4/CD8 migration. These secrete TNF-α, INF-γ, and IL-15 and result in inflammation. IL-15 is notable for its memory CD8 inducing effects.

The work-up for confirmation of a fixed drug eruption is a skin biopsy, a patch test on the previously affected area, and/or oral provocation of the suspected cause. The lesions will recur at the previously affected areas with re-exposure of the offending agent. Treatment includes systemic antihistamine, topical corticosteroid, avoidance of offending drug, and if infection is suspected: antibiotics and proper wound care. Both of the above patients had the offending drug withdrawn.

Sources:

1. Fidan V, Fidan T. Fixed drug eruption against rupatadine fumarate. J Craniofac Surg. 2011;22(5):1682-3.
2. Teraki Y, Shiohara T. IFN-gamma-producing effector CD8+ T cells and IL-10-producing regulatory CD4+ T cells in fixed drug eruption. J Allergy Clin Immunol. Sep 2003;112(3):609-15.
3. 20.Bolognia JL, Jorizzo JL, Rapini RP. Fixed drug eruptions. In: Dermatology. London, England: Mosby; 2003:344-5.
4. Ohtoshi S, Kitami Y, Sueki H, Nakada T. Utility of patch testing for patients with drug eruption. Clin Exp Dermatol. 2014;39(3):279-83.