This is a case of incidentally found hypothermia in a 26 year old male who was transferred from the prison infirmary for hematemesis during the month of May. He reports having chills for at least the last week with nausea and vomiting and development of hematemesis starting within the last 24 hours. Further questioning revealed that he had headaches, worsening lower extremity weakness, and urinary incontinence in the last several days. His initial temperature was 36° C but repeat readings were consistently around 30. His blood pressure was 124/91 with a heart rate of 60, respiratory rate of 15, and oxygen saturation of 98% on room air. His WBC was 6 with a normal differential. The prison infirmary stated that the patient’s only past medical history was possible sarcoidosis.

Hypothermia due to environmental exposure is often thought about, however, other causes include metabolic, neurologic, and sepsis. TB meningitis can cause hypothermia by direct involvement of the CNS or sepsis. TB can infiltrate the hypothalamus or causes hydrocephalus which places pressure on the hypothalamus, which is responsible for thermoregulation. Hypothermia due to sepsis is caused by a failure of vasoconstriction or by inducing an abnormality in the hypothalamic response via a cytokine response. Signs and symptoms of hypothermia can manifest in almost every organ system: Bradycardia and repolarization abnormalities are found in the cardiovascular system. Manifestations of the nervous system include ataxia, hyporeflexia, and decreased nerve conduction. Cold-induced diuresis is caused by the loss of the ability to reabsorb water and resistance for ADH. Ileus or punctate hemorrhages develop in the GI system.

In the case of this patient, TB infiltration of his basal ganglia and hydrocephalous were the causes of his hypothermia. With treatment of his meningitis his hypothermia and presenting symptoms did improve. Many of his presenting symptoms can be linked to manifestations of his hypothermia. His hematemesis was likely the punctate hemorrhages found with hypothermia. His new on-set urinary incontinence can be attributed to the cold-induced diuresis.

References
Chronic Kidney Disease in an Elderly Patient
Lucille Brunker\textsuperscript{1} C. P. Brunker\textsuperscript{1,2} 1 University of Utah School of Medicine, 2 Intermountain Healthcare, Salt Lake City, UT

History

90 year old woman with osteoporosis, chronic kidney disease, hypertension with lower extremity edema, mild dyspnea & feeling weak for past few weeks presents to her PCP.

ROS: no weight loss, falls, depression, other resp, CV & GI.

PMHx: chronic back pain, hx of vertebral fx’s, macular degeneration, polymyalgia rheumatica.

ADLS: independent in all IADLs: help with transportation, shopping, finances (decreased vision)

Meds: Calcium/Vit D 600 mg/1000 IU bid, Alendronate 70 mg/wk

Physical

General: Cheerful, energetic thin elderly woman, enjoying visiting with family

Vital Signs: 127/62, P 60, R 20, T 96.1, Ht 66” weight 125, BMI 20

Eyes: wears glasses, mono-ocular vision, 20/200

Pulm: normal respiratory mechanics, clear

CV: RRR Ext: 2+ bilateral pedal edema

Back: kyphosis, no vertebral tenderness to palpation

Geriatric Assessment: mini-cog unable to draw clock due to low vision, 3/3 recall, Oriented x 3

Differential Diagnosis

- Chronic glomerulonephritis
- Vasculitis
- Multiple myeloma
- Rheumatoid Arthritis
- Wegener Granulomatosis
- Infection
- Malignancy
- Acute Injury

Evaluation

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<th>DATE</th>
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<td>1.1</td>
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<td>Vit D 27 Ca 9.8, iPTH 56</td>
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<td>42</td>
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2/2011 Serum Immunofixation: IgG monoclonal protein, lambda light chain

Immunologic studies: neg except c-ANCA +

Radiology: Renal U/S kidneys normal in size and echotexture, no hydronephrosis, lesions, calculus & cortex well-preserved


Necrotizing glomerulonephritis 25/37, with crescents

H & E example from Stone, John H. - Rheumatology, 1547

Conclusions

The prevalence of chronic kidney disease (CKD) is growing most rapidly in people ages 60 and older. Following practice guidelines can result in significant cost savings, even in (or perhaps especially in) older adults. In accordance with recommendations, our patient was referred to nephrology where she received biopsy for diagnosis and was treated for Wegener’s Granulomatosis with prednisone and cyclophosphamide. Her therapy was adjusted to monotherapy with prednisone because of an adverse reaction to the cyclophosphamide. She had dramatic improvement in renal function, almost returning to baseline.

Progression of chronic kidney disease to end stage renal disease (ESRD) changes health care costs dramatically. In 2009, the cost for hemodialysis treatment at a clinic per patient was roughly $82,000, much greater expense than the cost to evaluate and treat our patient. In accordance with practice guidelines, early referral to nephrology resulted in improvement of her renal function to almost baseline and approximate $110,000 savings over 2 years and she reports excellent quality of life and maintenance of independence in ADLs.

References


Palmer SC. Craio JC. Navaneethan SD. et al. Benefits and harms of statin therapy for...
A Therapeutic Vaccine for Prevention of Metastatic Outgrowth of Breast Cancer
Kimberley Davenport, Atakan Ekiz, Alana Welm, PhD
Department of Oncological Sciences, Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah

**BACKGROUND**

Breast cancer is the second biggest cause of mortality in women with cancer – mostly as a result of metastasis. An estimated 40% of human breast tumors over-express a tyrosine kinase called Ron. The Ron-MSP pathway functions as a critical immunosuppressive signal between a tumor and the immune system, thereby promoting tumor growth and especially metastasis. Ron is a receptor tyrosine kinase that is expressed on a variety of cells, including immune cells and breast cancer cells. Targeted disruption of the Ron-MSP pathway has been shown to increase CD8+ cells and other immune cells, and reverse immunosuppression in mice. Therefore, inhibition of Ron translates to significantly lower metastasis. Our hypothesis is that inhibition of Ron (and thereby the Ron-MSP pathway) in conjunction with a therapeutic whole cell tumor vaccine, will produce even lower rates of both primary tumor growth and metastasis than inhibition of Ron alone.

**METHODS**

A total of 20 FVB mice were used for this cohort. Because a target antigen for breast cancer has not yet been identified, a whole cell tumor vaccine is used consisting of 1 million irradiated cells per injection. PyMT-MSP breast tumor cells were irradiated with 10,000 rads. Initial vaccination was administered subcutaneously to six female FVB Wild Type (WT) mice and six female FVB Ron knock out mice. Subsequent vaccinations were administered on day 5 and day 18. Vaccinated mice were administered with GM-CSF on day 5 and day 18. Whole cell irradiated tumor vaccination when used in conjunction with inhibition of the Ron-MSP pathway appears to slightly augment the vaccine. Vaccinated mice were assessed on day 5 and day 18. Along with assessing the number of lymphocytes activated, it also slightly increased effector cell toxicity. However, medullary sections showed no significant difference.

**RESULTS**

Vaccinated mice (both WT and Ron knock out) demonstrated a roughly three-fold increase in activated CD8+ cells in the spleen vs. the control mice vaccinated with HBSS. The largest increase in vaccinated spleen CD8+ cell markers was the INF gamma. However, peripheral blood did not show an increase in CD8+ cell markers. The INF gamma increase may be due to an increased expression of INF gamma. When comparing WT to Ron knock out mice, both the day 5 cohort and day 18 cohort showed no significant difference in higher immune markers.

**CONCLUSIONS**

Whole cell irradiated tumor vaccination when used in conjunction with inhibition of the Ron-MSP pathway appears to slightly augment the vaccine. Vaccinated mice were assessed on day 5 and day 18. Along with assessing the number of lymphocytes activated, it also slightly increased effector cell toxicity. However, medullary sections showed no significant difference.

**HYPOTHESIS**

If we add a Therapeutic Vaccine to mice growing PyMT-MSP tumors (irradiated dead PyMT-MSP tumor cells + adjuvant)

**WE EXPECT TO SEE:**

- Significantly lower metastatic growth in WT mice and Ron +/- mice
- Significantly less primary tumor growth in Ron +/- vs. WT
- Ron-MSP pathway promotes metastases
- Therefore a therapeutic vaccine given after tumor growth should Educate the T-cells on the cancer and Cause T-cell expansion Cause increase in Cytokines
- We will test our hypothesis in WT and Ron +/- mice
- We will measure T-cells (CD8+ and CD4+)
- We will measure cytokines (reflection of T-cell activity)
- We will test this vaccine with and without adjuvant

**VACCINE STUDY (D18)**

**SUBJECTIVE T Cells and Immune Markers as a Percentage**

<table>
<thead>
<tr>
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<th>Days post-treatment</th>
<th>Days to reach 30% Spontaneous metastasis</th>
<th>Survived vs. wt percent</th>
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</table>
| F19 wild type (WT) | 30 | 30 | 100%
| F19 Ron -/- (KO) | 30 | 30 | 60%
| F19 Ron +/+ (WT) | 15 | 15 | 60%
| F19 Ron +/+ (KO) | 15 | 15 | 100%

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| F19 Ron +/+ (KO) | 15 | 15 | 100%

**WHAT IS NEXT?**

- Vaccine using more time points
- Vaccine using adjuvant GM-CSF
- Use novel Ron Inhibitor drug with Vaccine
A 72 year-old man presented to the Emergency Department with a 3 day history of progressive dyspnea on exertion and hypoxia. He has a history of COPD and wears 2LPM of O2 at baseline, but was now using 4-6LPM to maintain his oxygen saturations. He also noted a cough productive of black-red sputum and wonders if it may be bloody.

He had recently undergone a left total knee replacement 1.5 months prior, which was complicated by a joint infection that grew meticillin sensitive Staphylococcus aureus. For unclear reasons, the patient was started on vancomycin for this infection. This was changed to daptomycin 9 days prior to admission after he exhibited symptoms consistent with red-man syndrome.

On exam, temp. 38.3 deg. C, BP 119/61, HR 109, and 92% on 4LPM of O2. He was a morbidly obese, pleasant gentleman who appeared in mild distress secondary to dyspnea, speaking in 3-5 word phrases. His lungs demonstrated mild end-expiratory wheezes and distant breath sounds with mildly increased work of breathing. His left knee demonstrated a healing surgical incision with no fluctuance, erythema, or drainage. He had 2+ pitting edema to the knee in bilateral lower extremities, with the remainder of the exam unremarkable.

Initial labs demonstrated a white count of 13.2 (69% PMNs, 10% lymphocytes, 13% monocytes, 6.5% eosinophils). Serum chemistries were notable for a sodium of 129, a creatinine of 1.39, and elevated ESR/CRP at 45 and 10.7 respectively.

A CXR demonstrated bilateral lung opacities (R>L) consistent with pneumonia (Figure 1). A CT pulmonary angiogram demonstrated no PE, and 34% eosinophils, cementing the diagnosis of eosinophilic pneumonia, likely secondary to daptomycin use. The patient was taken off HCAP therapy and started on systemic corticosteroids, with notable respiratory improvement over the ensuing 5 days.

The disease is characterized by fevers, diffuse pulmonary infiltrates, hypoxemia, and >25% eosinophils on BAL. Drug induced EP is suspected when there is: temporally related exposure to a possible drug, no other cause that can be identified, resolution after cessation of drug, and recurrence on re-challenge with the suspected drug (though this is not recommended in clinical practice!).

EP associated with daptomycin appears to be relatively rare, with 20 confirmed/probable case reports and 38 possible case reports. In 2010, the FDA issued a safety announcement highlighting the association of daptomycin with EP and added this to the Adverse Reactions section of the drug label.

Treatment involves discontinuation of daptomycin often in conjunction with systemic glucocorticoids, though there is no consensus on the appropriate dose or duration of therapy. Most individuals will make a full recovery, though ongoing need for corticosteroid therapy has also been described.

The mechanism of daptomycin toxicity is unclear. It is known to bind pulmonary surfactant, and it has been postulated to incite an eosinophilic response via accumulation in the alveolar spaces and antigen presentation by macrophages.
Mr. L is a 76 yo M with a history of atrial fibrillation and chronic systolic heart failure admitted to the internal medicine service from the dermatology clinic for evaluation and management of worsening lower extremity ulcers. The ulcers were located on both lower extremities (right greater than left) at the posterior calf and had been present for approximately 2 months.

Mr. L had previously been treated with antibiotic therapy for possible cellulitis without improvement. He had no prior history of skin breakdown or recurrent infections. One week prior to this admission, Mr. L had undergone repeat biopsy of the ulcer which showed microvascular thrombi. The patient was started on warfarin, but noted worsening of his ulcers shortly after. This prompted the patient’s current admission to internal medicine for further evaluation and management.

Medications at the time of admission included amiodarone, warfarin, allopurinol. Dapsone was discontinued prior to admission.

**Histology**

Mr. L presented with persistent lower extremity ulcers despite appropriate management of community acquired cellulitis. Biopsy results were concerning for microthrombi which prompted evaluation for coagulopathy. Initial results showed elevated anti-cardiolipin IgG and IgM.

Based on Sapporo Criteria, Mr. L met criteria for diagnosis of antiphospholipid syndrome.

1. **Clinical Feature:** Biopsy showing microthrombi, Livedo Reticularis
2. **Presence of autoantibody:** Anti-Cardiolipin Antibodies

Autoantibodies were repeated at 12 weeks and again showed elevated anti-cardiolipin Ab, confirming the diagnosis of antiphospholipid syndrome. ANA was negative and no other clinical or laboratory criteria was found to suggest SLE.

Mr. L was found to have subtherapeutic INR. It was thought that initiating warfarin without heparin bridging may have exacerbated his hypercoagulable state and led to worsening of the ulcers. He was placed on heparin therapy and bridged until warfarin was therapeutic. Ulcers improved following therapeutic anticoagulation.

**Summary**

Little Ulcer, Big Problem

Hannah Gaedtke, MD

University of Utah-Department of Internal Medicine

**History of Present Illness**

Mr. L is a 76 yo M with a history of atrial fibrillation and chronic systolic heart failure admitted to the internal medicine service from the dermatology clinic for evaluation and management of worsening lower extremity ulcers. The ulcers were located on both lower extremities (right greater than left) at the posterior calf and had been present for approximately 2 months.

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**Description of Ulcer per dermatology consult:**

Right lower posterior-medial leg, large tender malodorous ulcer down to subcutaneous fat with surrounding reticulated/livedo change. Base of ulcer with yellow fibrinous exudate. Anterior of leg with atrophic hypopigmented patches. Mild erythema surrounding wound, no undermined border.

**Labs, Pathology, Imaging**

**Labs:**
- ANA, Protein S/C, Anti-thrombin: WNL
- Lupus Anticoagulant not detected
- Beta 2 glycoprotein IgM, IgG, IgA: WNL
- Anti-Cardiolipin IgG: 25 (0-14)
- Anti-Cardiolipin IgM: 80 (0-12)

**Biopsy Results:**
- Many of the blood vessels show intraluminal fibrin thrombi. Other vessels show vasculitis with neutrophils and dust in vessel walls.

**Lower Extremity Duplex:**
- No thrombus of the right lower extremity.

**Differential Diagnosis**

1. Vasculopathy secondary to hypercoagulable state
2. Vasculitis
3. Calciphylaxis

**References**


Pruritic Purpura and Acute Respiratory Failure
Verena C. Haringer, M.D.
University of Utah, Department of Internal Medicine

Case Description
A 61 year old white male presented to the Emergency Department with a 6-month history of pruritic purpura in his bilateral lower extremities as well as polyarticular arthralgias and weight loss.

His only past medical history are multiple musculoskeletal injuries and a s/p septic arthritis in both knees. The patient endorses iv drug abuse in the past and cocaine abuse with the last use about 1 year prior to admission. His family history is positive for lymphomas in multiple relatives.

On admission he was found to have palpable, macular purpura on the dorsal hands and prominent on his bilateral legs, including the soles of his feet (Fig. 1), a 3 cm mobile, non-tender, soft mass on the right neck, periodontal disease with gingivitis, diffuse small oral ulcers, punctate oral hemorrhages, and an exudate on his right tonsil. Labs showed a WBC of 11.8 with 11% eosinophils, CRP of 10, a CK of 1300 and 5 RBC on UA. CT chest on admission showed scattered ground glass opacities (Fig. 3).

Fig. 1 courtesy of Brian J. Horner, M.D.; Fig. 2 courtesy of Scott R. Florell, M.D.; Fig. 3-5 courtesy of the University of Utah Hospital

Hospital Course
Extensive work-up revealed anemia, positive Hepatitis B core antigen IgM antibody, elevated rheumatoid factor and positive ANCA-PR3. Urine was initially negative for red cell casts. TTE/TEE showed no evidence of endocarditis, urine was negative for cocaine, SPEP was within normal range, cryoglobulins were negative.

A skin biopsy of the patient’s lower back showed leukocytoclastic vasculitis with IgM and C3 deposition (Fig 2). A biopsy of a lower lip ulcer showed eosinophil-predominant vasculitis.

On Day 11 after admission, the patient had to be transferred to the MICU for acute hypoxic respiratory failure requiring BiPAP treatment. He was found to have ARDS secondary to diffuse pulmonary hemorrhage (Fig. 4). At this time his urine was found to be positive for red cell casts as well as dysmorphic red cells, and the patient underwent renal biopsy which was inconclusive. Due to the acute worsening of the patient’s clinical picture, he was treated with a 3-day course of plasmapheresis and high-dose iv steroids, followed by po steroids and cyclophosphamide which led to an improvement of his respiratory function (Fig. 4).

Fig. 1
Fig. 2
Fig. 3
Fig. 4
Fig. 5

Differential Diagnoses
- Lymphoma
- Endocarditis with septic emboli
- Chronic hepatitis with cryoglobulinemia
- Henoch-Schönlein purpura preceded by oral infection
- Microscopic polyangiitis
- Churg-Strauss syndrome
- Levimasole-induced vasculitis in a patient with a history of cocaine abuse
- Granulomatosis with polyangiitis (Wegener’s)

Discussion
The overall clinical picture in this middle-aged white male points towards a small vessel vasculitis, most likely granulomatosis with polyangiitis (Wegener’s).

Although it is best to have a confirmation of diagnosis by tissue biopsy at a site of active disease, patients should be treated empirically if the clinical suspicion is high and initiation of therapy is life saving and organ sparing.

Fig. 1 courtesy of Brian J. Horner, M.D.; Fig. 2 courtesy of Scott R. Florell, M.D.; Fig. 3-5 courtesy of the University of Utah Hospital

References
3. Peng et al. Culture-negative subacute bacterial endocarditis masquerades as granulomatosis with polyangiitis (Wegener’s granulomatosis) involving both the kidney and lung. BMC Nephrol. 2012 Dec 26;13:74
Behcet’s disease with Crohn’s disease  
Abdul Haseeb, MD MPH  
University of Utah Department of Internal Medicine

Purpose/Methods
To describe the coexistence of “auto-inflammatory” Behcet’s disease with Crohn’s disease and to demonstrate clinical and diagnostic presentations that make it difficult to identify them as separate entities.
Retrospective chart review and bibliographic database search for relevant studies pertaining to the patient’s clinical presentation.

Case Discussion
37-year-old Hispanic male with a known history of Crohn’s disease presents with recurrent oro-genital ulcers, anterior uveitis, and papulopustular lesions. He had frequent Crohn’s flares since his initial diagnosis three years ago, despite being on maintenance mesalamine therapy and corticosteroid use during acute flares. He had failed 6-mercaptopurine treatment in the past due to liver toxicity and Infliximab treatment due to anaphylaxis. In addition to recurrent colitis, the patient presented with a plethora of extraintestinal findings including neutrophilic vasculitis, skin abscesses, sinusitis, nasal polyps, oral ulcers, pulmonary granulomas, granulomas on bone marrow biopsy, splenic granulomas, uveitis, and non-specific arthritis. He underwent an extensive rheumatological work-up and the top two differential diagnoses were Crohn’s disease with extra-intestinal manifestations and Behcet’s disease. Labs were significant for an elevated proteinase-3-antibody, but negative for ANA, and ANCA. Colonoscopy revealed inflammation in the terminal ileum and colitis in the ascending and transverse colon.

Although these findings were consistent with a Crohn’s flare, the patient was concurrently diagnosed with Behcet's based on his recurrent episodes of oral aphthae, genital aphthae, uveitis, and papulopustular skin lesions. Diagnosis was based on most widely accepted International Study Group (ISG) criteria for Behcet’s disease. He was initially started on Azathioprine, but treatment was complicated with the development of neutrophilic dermatoses leading to a diagnosis of drug induced Sweet's syndrome. Treatment was finally switched to cyclosporine and low dose prednisone. The patient has shown significant clinical response to this regimen and has had no readmissions with Crohn or Behcet’s flares.

Conclusions
A distinct diagnosis of Behcet’s disease or inflammatory bowel disease can be perplexing with a significant overlap in the systemic and gastrointestinal features of both disorders. Behcet’s disease classified as an auto-inflammatory disease, usually runs an abating course with time compared to lifelong course of Crohn’s. Although intestinal Behcet’s disease accounts only for a minimal 1-2%, the histological features closely resemble Crohn’s on endoscopy. The diagnosis of Behcet’s is based mainly on clinical findings due to lack of pathognomonic laboratory test. A few case reports are published describing the co-existence of Crohn’s disease with Behcet’s; these are mostly from Turkey and along the “silk route.” Familial studies reviewed also suggested a close relation between the two diseases indicating them to be part of spectrum rather than two distinct disease entities. Co-existent Crohn and Behcets’ disease should be considered a diagnostic possibility in patients who present with overlapping symptoms.

References
A 76-year-old male with CAD, hypertension and prostate cancer s/p prostatectomy presented with a 6-week history of progressively worsening back pain. This pain was initially associated with fevers and chills. He presented both to an InstaCare and an outside ED, where he was found to have a persistent leukocytosis prior to his current presentation in the IMC ED. Treatment of the prostate cancer (diagnosed in 1998) included surgery and androgen deprivation therapy.

He denied IV drug abuse. Further questioning also revealed a new complaint of chest pain exacerbated by deep breathing.

Imaging

The patient acutely developed aphasia, R facial numbness and R hand clumsiness. MRI brain demonstrated ischemia within territories of the L frontal lobe and punctate foci within the bilateral parietal lobes consistent with subacute stroke. In the following days, two further ASSERT calls were performed for similar symptoms. He was otherwise hemodynamically stable. Left heart catheterization was performed, demonstrating obstructive disease within the LAD.

By hospital day #9, the patient underwent mitral valve replacement and CABG (LIMA to LAD). Five days s/p CT surgery, he was discharged without further complication.

Diagnosis

#1. Infective endocarditis of the mitral valve, #2. L4-L5 osteomyelitis/discitis, #3. Acute coronary syndrome

Studies

References


Figure 2 image obtained from: www.vcu.edu

Thank you to Drs. Scott Woller and Corwin Edwards for obtaining the included Echo images.
Dental Appliances in the Treatment of OSA

Surabhi Kasera*, Scott Hollingshaus MD #, Krishna M. Sundar MD #, Gary Lowder DDS*, Julia Whitaker MD#
*Washington University in St. Louis, Departments of #Medicine & #Dentistry, University of Utah

Introduction

Dental appliances are recommended for patients with mild to moderate obstructive sleep Apnea (OSA) that are intolerant to continuous positive airway pressure (CPAP) therapy. The Sleep Wake Center (SWC) has a dental appliance program that custom-fits appliances for referred patients. This study measured the efficacy and follow-up of the TAP III dental appliance given to patients for OSA or upper airway resistance syndrome (UARS) in the last 2 years.

Objectives

1. Assess follow-up visit frequency, compliance with provider visits, and long-term care for patients on a dental appliance received through the SWC.
2. Assess efficacy of TAP III appliance based on patient-reported efficacy and objective follow-up measures.

Methods

Data on patients that received the TAP III device at the SWC within the last 2 years (since inception of EPIC electronic medical records) were reviewed. Demographic data and reason for dental referral were obtained from the medical records. Duration and frequency of follow-up after dental appliance application was obtained from EPIC. TAP III appliance efficacy in patients was assessed using the following:
- Patient and provider-reported subjective assessments of TAP III appliance efficacy.
- Oximetry and PSG findings while using the dental appliance.

Statistical analysis using a student’s t-test was done to find significant differences in TAP III efficacy with age, sex, BMI, etc. The results of this analysis was used to develop protocols for future follow-up of patients following dental appliance application.

Results

<table>
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<tr>
<th>Diagnosis</th>
<th>Compliance</th>
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<tr>
<td>Mild Sleep Apnea</td>
<td>25%</td>
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<tr>
<td>Moderate Sleep Apnea</td>
<td>54%</td>
</tr>
<tr>
<td>Severe Sleep Apnea</td>
<td>11%</td>
</tr>
<tr>
<td>Upper Airway Resistance Syndrome</td>
<td>33%</td>
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</tbody>
</table>

Conclusions

1. Efficacy of dental appliances is increased in obese subjects. This has been noted in prior studies as well.1-2
2. For patients receiving dental appliances at the SWC, significant deficiencies in follow-up care were noted in the following ways:
   a. Lack of follow-up with referring provider and with dentist fitting the appliance
   b. Lack of pre-defined objective testing and validated questionnaires to assess efficacy of dental appliance
   c. Lack of comprehensive program aimed at improving BMI along with dental appliance therapy for OSA or UARS patients

References

1. Use of Flow-Volume Curves to Predict Oral Appliance Treatment Outcome in Obstructive Sleep Apnea, American Journal of Respiratory and Critical Care Medicine 2007; 175: 726-730
2. Efficacy of an Adjustable Oral Appliance and Comparison with Continuous Positive Airway Pressure for the Treatment of Obstructive Sleep Apnea Syndrome, Chest 2011; 140: 1511-1516
Primary Sclerosing Cholangitis in the Setting of Normal Liver Chemistries
Can Be Associated with Severe Ductal Disease and Dominate Strictures

Thomas Queen, MD, Kristen Cox MS, RN, Douglas G. Adler, MD
Division of Gastroenterology, University of Utah Health Sciences Center, Salt Lake City, UT

INTRODUCTION

- Primary sclerosing cholangitis (PSC) is a chronic progressive disease characterized by inflammation, fibrosis and stricturing within the intra and extrahepatic biliary ducts.
- It is commonly associated with abnormal liver function tests such as alkaline phosphatase, AST, ALT and total bilirubin.
- A subset of PSC patients will present with normal laboratory studies.

OBJECTIVE

- The aim of this study is to evaluate patients with PSC with normal liver function tests.

METHODS

- We conducted a retrospective study of PSC patients with normal liver chemistries to evaluate their clinical course, endoscopic, and pathologic findings.
- This study was approved by the institutional review board at the University of Utah School of Medicine, Salt Lake City, Utah.
- We reviewed electronic medical records, procedure reports, imaging studies, and pathology reports on patients with known or suspected PSC between the period of February 2000 to April 2013.
- We also evaluated a prospectively evaluated database of PSC patients.
- Patients in this study were diagnosed with PSC by laboratory studies, liver biopsy, MRCP, ERCP, or a combination thereof.

RESULTS

- There were 102 PSC patients in our PSC database from 2000 to 2013.
  - 11 patients had normal liver chemistries at time of presentation (8M, 3F, mean age 47.1Y)
  - 5 patients had IBD: 3 out of 5 had Crohn’s disease (1 had colitis), 2 out of 5 had ulcerative colitis.
  - On CT scan, 8 out of the 11 patients had evidence of cirrhosis.
  - 8 out of the 11 patients underwent MRI/MRCP and 5 of these patients had ductal findings suggestive of PSC.
  - 1 patient had an MRI/MRCP that was suggestive of PSC and cholangiocarcinoma.
  - All 11 patients underwent ERCP which confirmed the diagnosis of PSC.
    - All 11 patients had intrahepatic ductal disease manifesting as innumerable strictures and pruning.
    - 4 patients were felt to have dominant strictures: 3 of these dominant strictures were in the common hepatic duct and 1 was in the common bile duct.
    - 3 patients were felt to have mild PSC, 6 were felt to have moderate PSC, and 2 were felt to have severe PSC.
    - There were no complications following ERCP.
  - 8 patients underwent tissue sampling by brushings and/or biopsy during ERCP.
    - 3 patients were not felt to warrant tissue sampling.
    - 1 patient had a mass lesion at the common hepatic duct that to date has yielded only benign brushing, histology, and FISH results.
    - The 1 patient with the dominant CBD stricture had brushing that showed atypical cells suspicious for malignancy and positive FISH study. This patient underwent a pancreaticoduodenectomy for presumed cholangiocarcinoma. Final pathology showed evidence of high grade dysplasia but no cancer.
    - None of the remaining patients who underwent tissue sampling had positive FISH testing or positive brushings for malignancy.

CONCLUSIONS

- PSC patients with normal serum liver chemistries has not been previously well described.
- PSC patients can have cirrhosis and significant ductal disease, including dominant strictures and abnormal tissue samples, in the setting of normal liver chemistries.
- Patients with PSC and normal liver chemistries were less likely to have IBD and colitis than were patients with PSC and abnormal labs.
- All patients tolerated ERCP exams without difficulty and had no complications: this may be explained, at least in part, by undergoing ERCP by experienced operators.
- No patient has had significant progression of disease over a mean follow up period of 50 months. This is in contrast to most PSC patients who can be expected to have progression when followed over the same timeframe.
Budd-Chiari Syndrome Secondary to Hepatic Zygomycosis in a Neutropenic Patient
Craig D. Robison,1 Bert K. Lopansri1,2
1Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, Utah; 2Department of Infectious Disease, Intermountain Healthcare, Salt Lake City, Utah

Introduction

Zygomycosis is a devastating fungal infection, mostly seen in immunocompromised persons and diabetics. Mostly associated with rhino-orbital-cerebral and pulmonary infections but occasionally can be found in other organ systems. Mortality remains extremely high despite treatment.

A 46 year old previously healthy female underwent idarubicin and cytarabine induction chemotherapy for newly diagnosed AML M2.

On day #7 She developed neutropenic fever and vancomycin and cefepime were empirically started with evidence for central venous catheter (CVC) exit site infection. Blood cultures were negative. Fungal biomarkers were obtained on day #11 and yielded a negative 1,3 Beta D-glucan and a weakly positive Galactomannan initially thought to be a false positive from total parenteral nutrition. On day #16 the patient developed worsening abdominal pain. Mucafungin dosing was increased and metronidazole was added. On day #17 the patient developed elevated LFTs (normal on day #14) and liver failure. Mucafungin was replaced with liposomal amphotericin B.

CT imaging demonstrated mild colitis of the descending and sigmoid colon along with multiple new large hepatic and intra-abdominal hypodense masses extending into the suprarenal IVC thought to be leukemic tumors vs. infectious etiology, most likely mucormycosis.

She rapidly developed septic shock, ascites, encephalopathy, respiratory failure, and renal failure requiring transfer to the intensive care unit, intubation, and hemodialysis. Surgery was not possible due to progressive decline. Her LFTs continued to increase consistent with fulminant hepatic necrosis. Care was withdrawn at the family’s request and the patient expired on day #21.

Autopsy limited to the liver demonstrated massive hepatonecrosis secondary to portal vein thrombosis and extensive venous thrombosis with broad, irregularly shaped, largely aseptate hyphae, some with right angle branching, consistent with mucormycosis. Leukemic infiltrates into the liver were not identified. Mechanism of hepatic involvement remains unexplained but may be related to extension from colitis or dissemination from CVC exit site infection.

We present a case of fatal hepatic necrosis from Budd-Chiari syndrome attributed to angioinvasive mucormycosis in a patient undergoing chemotherapy for AML. Diagnosis was confirmed only at time of autopsy, but imaging helped narrow the differential when vascular invasion was seen. Despite timely diagnosis and initiation of systemic antifungal therapy this patient expired. Surgery was not an option given hemodynamic instability, extensive liver involvement and chemotherapy-induced pancytopenia.

Table 1. Patient’s lab results on days #1, #14 and #17.

| Day #   | WBC (K/μL) | Hgb/Hct (g/dL; %) | Plts (K/μL) | Na+ (mmol/L) | K+ (mmol/L) | CO2 (mmol/L) | BUN/Cr (mg/dL) | Alk Phos (U/L) | AST (U/L) | ALT (U/L) | T Bil (mg/dL) | ALP (U/L) | INR
|---------|------------|-------------------|------------|-------------|-------------|-------------|---------------|---------------|-----------|-----------|-------------|----------|-------
| 1       | 4.5        | 9.9-29            | 94         | 139         | 4.1        | 25          | 12/0.52       | 88            | 107       | 23        | 25          | 1.1      | Neg  
| 14      | 0.2        | 9,527.5           | 43         | 140         | 3.6        | 33          | 10/0.30       | 132           | 107       | 33        | 55          | 0.2      | Neg  
| 17      | 0.1        | 8.6/249           | 9          | 134         | 5.2        | 27          | 29/1.48       | 107           | 23        | 27        | 8.904      | 5.7      | Neg  

Zygomycosis

- Zygomycetes is a class of fungi include the following species: Mucor, Rhizomucor, Rhizopus, Absidia
- Angioinvasion leading to tissue necrosis is a hallmark of zygomycosis.
- Healthcare-associated infections have been reported
- Gastrointestinal mucormycosis thought to be secondary to translocation of ingested spores
- Pooled mortality > 50% despite treatment with histopathology
- Fungal cultures often negative
- Treatment involves aggressive surgical debridement and antifungal therapy
- Duration of therapy is variable and cure requires recovery of neutrophil function
- Prognosis is very poor despite early appropriate treatment

Discussion

- Fewer than 15 cases reported in the literature
- Mostly in patients with hematological malignancies (AML, ALL), solid organ transplant recipients, and diabetics
- Pooled mortality > 50% despite treatment with amphotericin

We present a case of fatal hepatic necrosis from Budd-Chiari syndrome attributed to angioinvasive mucormycosis in a patient undergoing chemotherapy for AML. Diagnosis was confirmed only at time of autopsy, but imaging helped narrow the differential when vascular invasion was seen.
ACE-I/ARB Administration following Cardiac Catheterization Is Associated with Reduced Contrast-Induced Nephropathy

Craig D. Robison², MD; Heidi T. May¹, MSPH; Benjamin D. Horne¹, PhD; MPH; Donald L. Lappe¹, MD; Joseph B. Muhlestein², MD; Jeffrey L. Anderson², MD
¹Intermountain Heart Institute, Intermountain Medical Center, Murray, Utah; ²Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, Utah

Background

Contrast-induced nephropathy (CIN) is a complication of cardiac catheterization. Angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) are frequently prescribed in those undergoing cardiac catheterization. Studies evaluating ACE/ARB use and cardiac catheterization thus far have produced mixed results on the effect of these medications on contrast-induced nephropathy.

Objective

To evaluate the association between ACE-I and ARB administration and development of contrast induced nephropathy following cardiac catheterization.

Methods

5,091 patients in the Intermountain Heart Collaborative Study Registry (Salt Lake City, UT) undergoing cardiac catheterization were evaluated for administration of ACE-I/ARB prior to discharge following cardiac catheterization. Patients with baseline creatinine ≥ 2.5 mg/dL were excluded. Follow-up for one year included the evaluation for development of CIN within 10 days:
- Increase in baseline creatinine ≥ 0.5 mg/dL OR
- Increase in baseline creatinine ≥ 25% mg/dL OR
- Absolute increase of ≥ 0.5 mg/dL

Evaluated for persistent CIN between 6-12 months:
- Persistent Δ in Creatinine ≥ 0.5 mg/dL from baseline

Perform multivariable logistic regression analysis, adjusting for cardiovascular risk factors, baseline creatinine, contrast amount, medications, and CAD status.

Results

Table 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No-ACE-I/ARB</th>
<th>ACE-I/ARB (n=2020)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.1±13.3</td>
<td>68.0±12.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>65.1%</td>
<td>67.2%</td>
<td>0.048</td>
</tr>
<tr>
<td>Hypertension</td>
<td>57.9%</td>
<td>68.5%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>34.9%</td>
<td>42.4%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking</td>
<td>24.9%</td>
<td>30.3%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Family History CAD</td>
<td>35.1%</td>
<td>37.4%</td>
<td>0.005</td>
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<tr>
<td>Ethnic Status</td>
<td>12.8%</td>
<td>12.9%</td>
<td>0.52</td>
</tr>
<tr>
<td>Road Failure</td>
<td>1.5%</td>
<td>1.1%</td>
<td>0.17</td>
</tr>
<tr>
<td>Prior MI</td>
<td>14.8%</td>
<td>17.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prior CAD</td>
<td>4.7%</td>
<td>5.8%</td>
<td>0.18</td>
</tr>
<tr>
<td>Prior A-Fib</td>
<td>18.9%</td>
<td>18.0%</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Figure 1. Kaplan-Meier 1 year event-free survival for (A) Death, (B) Myocardial Infarction, (C) Revascularization, and (D) New Onset Atrial Fibrillation for patients receiving ACE-I/ARB and controls.

Table 2. Characteristics No ACE-I/ARB ACE-I/ARB (n=2628) p-Value

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No-ACE-I/ARB (n=2463)</th>
<th>ACE-I/ARB (n=2628)</th>
<th>p-Value</th>
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<tr>
<td>Age (years)</td>
<td>64.2%</td>
<td>48.7%</td>
<td>&lt;0.0001</td>
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<tr>
<td>Sex (male)</td>
<td>54.9%</td>
<td>52.4%</td>
<td>&lt;0.0001</td>
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<tr>
<td>Hypertension</td>
<td>64.2%</td>
<td>46.2%</td>
<td>&lt;0.0001</td>
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<tr>
<td>Diabetes</td>
<td>40.9%</td>
<td>40.9%</td>
<td>0.17</td>
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<tr>
<td>Smoking</td>
<td>24.7%</td>
<td>26.3%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Family History CAD</td>
<td>64.2%</td>
<td>49.7%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 3. Baseline Characteristics of the Study Population

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<tr>
<th>Characteristics</th>
<th>No-ACE-I/ARB</th>
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<td>0.18</td>
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<tr>
<td>Prior A-Fib</td>
<td>18.9%</td>
<td>18.0%</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Discussion

ACE-I/ARBs following cardiac catheterization were associated with decreased incidence of CIN despite more comorbidities and more contrast used. Literature reports evidence both for and against a renoprotective effect of ACE-I/ARBs in the development of contrast-induced nephropathy. Possible renoprotective mechanisms include opposing arteriolar vasoconstrictive effects of contrast media and attenuating contrast-induced renal tubular cell apoptosis.

Most other studies are limited by small sample sizes and short follow-up.

Randomized controlled trials are needed to clarify conflicting results in the literature.

References


Drug Rash  
Jennifer A Springer, MD  
University of Utah Department of Internal Medicine/Intermountain Medical Center

<table>
<thead>
<tr>
<th>HPI</th>
<th>Images</th>
<th>Diagnosis</th>
<th>Discussion</th>
<th>Hospital Course</th>
<th>Exam and Labs</th>
<th>References</th>
</tr>
</thead>
</table>
| 61 yo F presented to clinic with a full body rash and fevers. | ![Image 1] | Toxic Epidermal Necrosis (TENS) | - Most likely causative agents are Xarelto and Diltiazem. The onset of the rash was later than would be expected for Xarelto but sooner than would be expected for Diltiazem.  
- There are reports of SJS/TENS from Diltiazem and rare reports of SJS/TENS from Xarelto.  
- If there was no involvement of oral mucosa, the diagnosis would be Acute Generalized Exanthematous Pustulosis (AGEP). Patient did not have elevation of liver enzymes or other evidence of systemic involvement to raise concern for DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms). Vasculitides are common with hepatitis C, the status of her hepatitis is unknown, but there was no evidence of vasculitis on exam or biopsy.  
- There is mixed data for the use of oral steroids to treat drug rashes. | - All non-essential medications held. Dermatology consulted.  
- Treated with PO and topical steroids.  
- Xarelto discontinued, treated DVT with heparin drip and restarted Coumadin.  
- Swab of leg pustule grew MRSA. MRSA cellulitis treated with Cefotaxime.  
- Patient remained hemodynamically stable. WBC trended up to a max of 30,000/uL before trending down, no eosinophilia.  
- Rash quickly resolved, patient had near complete desquamation of epidermis. | ![Image 2] | ![Image 3] | ![Image 4] |
| Patient was diagnosed with a DVT, treated with Coumadin and Lovenox. | ![Image 5] | 1. "Severe Adverse Cutaneous Reactions to Drugs" NEJM Nov 1994  
2. "Cutaneous Adverse Reactions Associated with Calcium Channel Blockers" Arch Intern Med 1989  
3. "Xarelto (Rivaroxaban) Prescribing information" Janssen Pharmaceuticals Aug 2013  
4. Emedicine.medscape.com  
5. UpToDate.com |
| One week later she developed skin lesions concerning for skin necrosis; anticoagulation was changed to Xarelto. | ![Image 6] | | | | | |
| Two weeks after starting Xarelto, she was started on Diltiazem for HTN. | ![Image 7] | | | | | |
| The next day she developed a full body rash that started in the extremities and spread to her trunk. The rash was pruritic and associated with fevers. Patient stopped Diltiazem but rash continued to worsen. | ![Image 8] | | | | | |
| Past medical history significant for CAD, DM, COPD, HTN, hepatitis C, chronic kidney disease and multiple drug allergies - mostly to antibiotics. | ![Image 9] | | | | | |

Exam: T 37.7, HR 94, BP 146/75, RR 16, O2 sat 95% on 4L NC  
Morbidly obese female, skin had a maculopapular rash that coalesced into erythematous plaques on the trunk with skin desquamation. Lower extremities had bullae and pustules. 0.5 cm ulceration under tongue.  
Labs:  
Na 134, K 4.7, Cl 94, Bicarb 31, BUN 42, Cr 1.69, Glu 232  
Ca 9.1, Prot 7.6, Alb 3.7, AST 55, ALT 33, Alk Phos 128, Bili 0.8  
WBC 18, Hgb 11.2, Plt 378  
CRP 10.8, ESR 66  
Biopsy:  
Spongiform eosinophilic dermatitis with dermal perivascular neutrophils consistent with drug rash.
Small Vessel Vasculitis—No Small Thing

Miguel G. Teixeira, BS, MSIV. Internal Medicine. University of Utah, Salt Lake City, UT.

PHYSICAL EXAM

Vital Signs: T 37.3 HR 93 RR 20 BP 113/53 SpO2 92% RA

General: Alert and Oriented x4. NAD. Patient is tearful.

HEENT: No scleral icterus. No conjunctivitis. No rhinorrhea. Small 2-5mm erosions (A) on the soft palate, upper gingiva and lower lip mucosa.

Neck: Supple without lymphadenopathy.

Heart: Regular rate and rhythm, no murmurs or gallops.

Lungs: CTAB, no wheezes or crackles.

Abdomen: Soft, non-distended, non-tender. Nonrreative bowel sounds.

BACK: No CVA tenderness. No point tenderness along the spine.

Skin: Discrete, small purpuric macules in palmer aspect of digits. (B) Many non-blanchable palpable purpuric maculopapular lesions on both feet extending to the thighs with several weeping bullae and vesicles with serous fluid. (C, D) Minimal tenderness to palpation. Bilateral peripheral edema up to knees. Right medial thigh incision with stiches in place from biopsy.

LABS

ESR 34

CRP 14.5

INR 1.5

Lactate 1.5 Normal Differential

ANA negative, RF 15, c-ANCA negative

Hep C negative

Cytofibrinogen negative

Tox Screen: Negative other than for opiates

UA: Hgb +, Protein 1+, WBC 8/hpf, RBC 3/hpf

DISCUSSION

The patient was a previously healthy 63-year-old woman who presented with clinical stigmata of Henoch-Schönlein Purpura (HSP) including non-blanchable palpable purpura of her lower extremities, hematuria and proteinuria, GI involvement (mouth ulcers) and arthralgias with joint swelling. In addition to physical exam findings and abnormal UA, patient had elevated inflammatory markers with skin biopsy showing small vessel vasculitis with IgA and C3 deposition confirming leukocytoclastic vasculitis (LCV)-HSP.

HSP is a systemic, immune complex–mediated, leukocytoclastic vasculitis that presents acutely with an incidence in the adult population of 2-5/1,000,000 yearly. It is usually associated with a history of an upper respiratory illness (which this patient did not have) and is by far predominately a pediatric disease. Patients with Henoch-Schönlein purpura always present with a purpuric rash, 75% develop arthritis, 65% have GI involvement (usually abdominal pain) and 50% develop renal disease. It is usually a self limited disease (90%) treated with supportive care and oral steroids for joint pain alone. End-stage renal disease is a fairly uncommon occurrence (5%) although it is more likely to occur in the adult population.

Other forms of LCV were considered in our differential. Our patient did not have an elevated ANA or Hep C titer, making lupus or cryoglobulinemia unlikely. She also did not have signs of systemic infection or a history of new medications as etiologies for small vessel vasculitis. Of note however, patient’s recent exposure to pesticides and fertilizer prompted the question whether this could be a chemical/environmental hypersensitivity vasculitis. There have been several studies including a systematic review and two case-control studies that show an association between organic solvents, silica, and allergens found in the farming industry with primary vasculitis.

Although this evidence does not show causation of farming chemicals and IgA vasculitis, such chemicals should be considered when working with patients new to the farming industry.

References


Szasz I. Kosztolanczyk M. Et Al. Mechanisms Underlying Early Crp. Albiyin II: Bnp-Pa and Sdr-CrCmpm Cells. Pros for really liking me as a part of Medicine as a student.
When Macrophages Attack!

Madeline Torres BS, Matthew Feurer, MD, Shiven Patel, MD

University of Utah Health Sciences Center, Dept. of Internal Medicine, Division of Hematology, Salt Lake City, Utah

Laboratory Data

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin</td>
<td>153/12 mg/dL</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>123 mg/dL</td>
</tr>
<tr>
<td>D-dimer</td>
<td>7.8 um/L</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>317 mg/dL</td>
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<tr>
<td>PT</td>
<td>1.1 sec</td>
</tr>
<tr>
<td>INR</td>
<td>2.7 ratio</td>
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<tr>
<td>PTT</td>
<td>35 sec</td>
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<tr>
<td>IgA</td>
<td>125 mg/dL</td>
</tr>
<tr>
<td>IgM</td>
<td>2710 mg/dL</td>
</tr>
<tr>
<td>Hep A, IgM</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Serum IL-2 R 2390 pg/mL
Ferritin 53612 ng/mL
Fibrinogen 123 mg/dL
D-dimer 7.8 um/L
Triglycerides 317 mg/dL
PT 1.1 sec
INR 2.7 ratio
PTT 35 sec
IgA 125 mg/dL
IgM 2710 mg/dL
Hep A, IgM Negative

Serum IL-2 R 2390 pg/mL
M TB amp CSF negative
Histoplasma positive
Y/M CSF <1:2,
CSF R/B 4%
CSF glucose 41 mg/dL
CSF protein 22 mg/dL

Diagnostic Workup

After extensive medical evaluation, three diagnostic possibilities were raised: CNS tuberculosis (TB), Adult-onset Still’s disease, and Hemophagocytic Lymphohistiocytosis (HLH). Given the concern for TB she was started on pyrazinamide, rifampin ethambutol and isoniazid. Immunosuppressants that would have been appropriate for treatment of the other possible diagnosis were held given concern that these medicines would worsen a tuberculosis infection. Our patient represented two weeks later with a deteriorating clinical status. It was felt at that time that she most likely did not have TB and her care was focused on HLH that was likely triggered from a rheumatologic disorder. She was started on daily dexamethasone 10mg/m2. Clinical parameters such as joint pain, rash, fever curve, and splenomegaly were monitored for improvement. Abnormal laboratory parameters such as platelet count, elevated PT and aPTT, liver function tests, ferritin, and soluble IL-2 receptor levels were closely monitored for normalization.

Diagnosis

Hemophagocytic Lymphohistiocytosis

Discussion

HLH is a syndrome characterized by a constellation of 8 clinical criteria that include: fever >38.5, splenomegaly, cytopenias, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in bone marrow, spleen, lymph nodes or liver, low or absent NK-cell activity, elevated ferritin and sCD24 levels. The genetic form of this disease is inherited in an autosomal recessive manner which most often presents in the pediatric population, but has been initially diagnosed in adulthood.

Specific molecular mutations include PRF1, UNC13D, Munc18-2, Rab27a, STX11, SH2D1A, and BIRC4. Although multiple mutations have been identified, they share a common phenotype of impaired cytotoxic function of NK and T cells. The genes may affect granule-dependent lymphocyte cytotoxicity by impairing trafficking, docking, exocytosis priming or membrane fusion of cytolytic granules. The genetic defect may also impair the pathway by loss of functional perforin. This leads to the impaired elimination of activated macrophages by NK and T cells. These persistent macrophages not only phagocytize normal hematopoietic cells but also produce excess cytokines that lead to tissue damage throughout the body.

More commonly, adult HLH is secondarily acquired after a strong immunological activation. The most common triggers are infections (viral, more so than bacterial or fungal), hematologic malignancy such as leukemia or lymphoma, and autoimmune disease. In our patient’s case we felt that she most likely had a macrophage activating syndrome triggered by her known psoriatic arthritis. Therefore she was treated with steroids in hopes of controlling both her rheumatologic condition and HLH. Inadequate response would require standard induction per the HLH-94 protocol with dexamethasone and etoposide.

Antagonists to IL-1 and IL-6 have been reported to be helpful in patients with HLH secondary to rheumatologic disease as well. Untreated, the average survival of patients with HLH is 2 months. With treatment however, a survival rate of 55% after a mean follow-up of 3.1 years is reported.

Patients with HLH can present in many forms: fevers of unknown origin, hepatitis with acute liver failure, bone marrow failure, multiple skin manifestations, pulmonary dysfunction, sepsis-like physiology, cardiac and neurological abnormalities. Our patient obtained an initial diagnosis of CNS tuberculosis, leading to exacerbation and delay in treatment of her HLH. We present this case to increase the recognition of HLH. Prompt recognition and treatment are critical for this otherwise uniformly fatal disease.

References

Gluteal Diffuse Large B-cell Lymphoma presenting with Hypercalcemia
Khine Win, MD
University of Utah, Department of Internal Medicine

History of Present Illness
- A 59 year-old man with no significant past medical history presented with four weeks history of:
  - Bilateral leg weakness
  - Left buttock pain and swelling
  - Constipation
  - Mild confusion
  - Weight loss
- Previously treated with prednisone and narcotics as outpatient without any improvement

Diagnostic Lab and Imaging
- The large gluteal mass biopsy showed the diffuse large B-cell lymphoma (DLBCL), confirmed with positive CD20 and CD45 antigens. Fortunately, he has the localized disease on PET CT scan with no bone marrow involvement, based on the normal bone marrow biopsy and flow cytometry.
- CT pelvis showed the marked asymmetry of the pelvis with soft tissue attenuation mass on the left buttock, extending medially.

Discussion
- Severe hypercalcemia at presentation with very low parathyroid hormone level indicated the malignancy-associated hypercalcemia. He was treated with IV fluid hydration, zolendronic acid and calcitonin. His calcium level was normalized at discharge.
- Hypercalcemia is not a common presentation for non-Hodgkin lymphoma such as DLBCL. Only up to 13% of incidence was reported previously in the literature. Elevated parathyroid hormone-related protein (PTHrP) and bone metastases are the two most common etiologies responsible for malignancy-associated hypercalcemia. Interestingly, our patient has no bone metastases and low PTHrP level at presentation.
- Even though PTHrP is the most common humoral mediator in all malignancies, the ectopic calcitriol was reported to be a key mediator responsible for the malignancy-associated hypercalcemia in 30-40% of non-Hodgkin lymphoma. Calcitriol may be secreted by the lymphoma-associated macrophages and increased the intestinal absorption of calcium, leading to hypercalcemia. Unfortunately, the calcitriol level was not measured during the admission.
- The receptor activator of nuclear factor-κB (RANK) and its ligand, RANKL, are known to be involved in the osteoclastic bone resorption, releasing calcium from the bone. RANKL is secreted by the activated lymphocytes and its expression was upregulated by the PTH, PTHrP, calcitriol and prostaglandins. Other cytokines such as IL-1, IL-6, tumor necrosis factor-α (TNF-α), macrophage inflammatory protein-1 alpha (MIP-1α), MIP-1β were also reported to increase the local osteolysis in diffuse large B-cell lymphoma cells.

Conclusion
- Malignancy-associated hypercalcemia can be life-threatening without the urgent intervention.
- As we are learning more about the molecular pathophysiology of the bone resorption, many new targeted therapies for the malignancy-associated hypercalcemia, such as monoclonal anti-RANKL antibody (denosumab) and the decoy receptor (osteoprotegerin), have been identified.
- Trials to compare the new targeted therapies with the traditional bisphosphonate therapy such as zolendronate, are underway.

References

All biopsy and radiographic images were obtained through the courtesy of Dr. Corwin Edwards and Intermountain medical center.