Chicago Dermatological Society

April 2012
Monthly Educational Conference

Program Information
Continuing Medical Education Certification
and
Case Presentations

Wednesday, April 11, 2012
Stroger/Cook County Hospital
Sidney Barsky Lecture

Conference Host:
Division of Dermatology
Stroger Cook County Hospital
Chicago, Illinois

Program

Conference Locations

Stroger Cook County Hospital; 1900 W. Polk, Chicago
Main hospital – entrance corner of Ogden & Damen or through the CCH parking garage
Hektoen Institute – 627 S. Wood St., 1st Floor Lobby & Auditorium

Parking:
Cook County Hospital Garage: entrance on Polk St.
Alternate Parking: Rush Medical Center - Harrison just west of Ashland

Registration Area – beginning at 8:00 a.m. (sign-in sheets, name badges, exhibitors)
Lobby area of the Hektoen Institute; 627 S. Wood

Please note: Protocol books will be distributed in the Dermatology Clinic, Main Hospital until 10:30 a.m., and then at the registration area. Registration will be located at the Hektoen Institute only. You may proceed directly to the clinic and register later, if you prefer.

Program Events

8:00 a.m.	Registration Opens for All Attendees *Hektoen Institute, 1st floor lobby*
9:00 a.m. - 10:00 a.m.	**Resident Lecture** – *Hektoen Auditorium* "Clinical-Pathologic Correlations in Cutaneous Lupus Erythematosus" *Richard D. Sontheimer, MD*
9:30 a.m. - 10:45 a.m.	**Clinical Rounds** Patient & Slide Viewing *Dermatology Clinic "G", 2nd floor, main hospital; use elevator #1*
11:00 a.m. - 12:15 p.m.	**General Session** - *Hektoen Auditorium* BARSKY LECTURE: "Evolution of Thought Concerning Subacute Cutaneous Lupus Erythematosus and Clinically-Amyopathic Dermatomyositis" *Richard D. Sontheimer, MD*
12:15 p.m. - 12:45 p.m.	Box Lunches & visit with exhibitors *Hektoen Institute Lobby*
12:45 p.m. - 1:00 p.m.	**CDS Business meeting** – *Hektoen Auditorium*
1:00 p.m. - 2:30 p.m.	**Case Discussions** – *Hektoen Auditorium*
2:30 p.m.	**Meeting adjourns**

Mark the Date!

Next CDS monthly meeting – Wednesday, May 16, 2012 at the Rush University

Watch for details on the CDS website: www.ChicagoDerm.org

Guest Speaker

RICHARD D. SONTHEIMER, MD

Clinical Professor of Dermatology
University of Utah School of Medicine
Salt Lake City, UT

Delivering the Sidney Barsky Lecture

Dr. Sontheimer completed medical school at the University of Texas Southwestern Center in Dallas in 1972. He completed an internship and residency in internal medicine at the University of Utah prior to finishing his dermatology clinical and research training at UT Southwestern in 1979. He served as a full-time faculty in the Departments of Dermatology and Internal Medicine at UT Southwestern for 18 years. Beginning in 1998, Dr. Sontheimer served as the Head of the Department of Dermatology at University of Iowa Hospitals and Clinics for six years before pursuing a research sabbatical at the Hammersmith Hospital in London in 2004. He joined the University of Oklahoma Department of Dermatology in 2005 as its Vice-Chair, Director of Research, and Residency Director. He joined the Dept. of Dermatology at the University of Utah in 2009 as a clinical professor with a focus on patient care and clinical education/scholarship.

Dr. Sontheimer has had a career-long interest in the cutaneous manifestations of autoimmune connective tissue diseases. He also cares for individuals with other forms of rheumatologic skin disease including morphea/scleroderma and vasculitis. Dr. Sontheimer is recognized internationally for his clinical expertise in caring for individuals with these types of skin disorders.

CME Financial Disclosure: Dr. Sontheimer has no significant financial relationships to disclose.

Continuing Education Credit

Chicago Dermatological Society

"Chicago Dermatological Society Monthly Conference"

April 11, 2012 *Chicago, IL*

Participants must attend entire session to receive all types of credit. CFMC hosts an online evaluation system, certificate and outcomes measurement process. Following the conference, you must link to CFMC's online site (link below) to complete an evaluation form, in order to receive your continuing education statement of hours (certificate). Once the evaluation form is complete, you will automatically be sent a copy of your certificate via email.

Continuing Education evaluation and request for certificates will be accepted up to 60 days post activity date. The Colorado Foundation of Medical Care (CFMC) will keep a record of attendance on file for 6 years. CFMC contact information: 303-695-3300, ext. 3139.

Link address to evaluation form:
www.yourcesource.com/eval?act=647!04112012

JOINT SPONSOR STATEMENT

This Continuing Educational activity is Joint-sponsored by the **Colorado Foundation for Medical Care, Office of Continuing Education** and the **Chicago Dermatological Society**. **CFMC is accredited by the ACCME to provide continuing medical education for physicians.**

GOAL / PURPOSE

To broaden the clinical knowledge of dermatologists with respect to diagnostic.

SESSION OBJECTIVES

Upon completion of sessions, participants will be able to apply new knowledge and skills in the area of physician learning.

1. Describe the optimal diagnosis and management of patients presenting with sub acute cutaneous lupus erythematosus.
2. Discuss the hallmark cutaneous features of dermatomyositis and how to incorporate optimal diagnosis and management of these patients in a dermatological practice..

.CREDIT STATEMENTS

CME CREDIT

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through joint sponsorship of the Colorado Foundation for Medical Care, Office of Continuing Education (CFMC OCE) and Chicago Dermatological Society. CFMC is accredited by the ACCME to provide continuing medical education for physicians.

The Colorado Foundation for Medical Care designates this Live Activity for a maximum of 5.0 *AMA PRA Category 1 Credit(s) ™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

OTHER HEALTH CARE PROFESSIONALS

This educational activity has been planned and implemented following the administrative and educational design criteria required for certification of health care professions continuing education credits. Registrants attending this activity may submit their certificate along with a copy of the course content to their professional organizations or state licensing agencies for recognition for 5.0 hours.

DISCLOSURE STATEMENTS

All other members of the faculty and planning team have nothing to disclose nor do they have any vested interests or affiliations. **It is the policy of the Chicago Dermatological Society and Colorado Foundation for Medical Care (CFMC) that the faculty discloses real or apparent conflicts of interest relating to the topics of the educational activity.**

Case Presentations

CHICAGO DERMATOLOGIC SOCIETY

**We extend our sincere thanks to
Dr. Darryl Bronson and Dr. Jesse Jiang
for their review of the histopathology.**

Therapeutic Conundrums for Dr. Sontheimer

Three dermatomyositis cases will be presented to Dr. Sontheimer for treatment suggestions.

Patient A

62 year-old female with dermatomyositis, diagnosed by muscle and skin biopsy at an OSH in 2005, is being presented for treatment suggestions regarding her ongoing muscle and skin disease. She has never reached complete remission. Her case has been complicated by interstitial lung disease (DLCO 56%) and CT evidence of fibrosis and pulmonary hypertension. She was previously treated with IVIG for one year (unknown regimen, 2007, OSH), cyclosporine 150mg BID, and azathioprine 100mg BID. Her current regimen includes oral prednisone 7.5 mg daily, mycophenolate mofetil 1500mg BID, and methotrexate 20mg weekly, but she still has active skin disease and muscle weakness (albeit a normal CK, likely some component of steroid myopathy). The chronic steroids have also lead to diabetes, cataracts, several bone fractures, and osteoporosis (last T score -2.5). A systemic work-up for associated diseases has been negative.

What other treatment approaches are available for this patient?

Patient B

33 year-old female with amyopathic dermatomyositis, diagnosed by clinical findings and skin biopsy in 2010, is being presented for treatment suggestions for her recalcitrant skin disease. Her case has been complicated by a positive ANA (>1:160) with leukopenia, suggesting a possible overlap syndrome. She developed a rash on hydroxychloroquine 200mg BID (after 6 weeks) and is currently off oral prednisone. She is being treated with methotrexate 25mg weekly and topical clobetasol 0.05% ointment for her skin disease. A systemic work-up for associated diseases has been negative.

What other treatment approaches are available for this patient without muscle disease?

Patient C

82 year-old female with dermatomyositis, diagnosed in 10/2008 by muscle biopsy, and secondary interstitial lung disease that requires home oxygen (2L/min during exertion and 3L/min at night) is being presented for treatment suggestions for her lung disease. Jo-1 antibody testing was negative on two occasions. Her DLCO is severely reduced (32%) and imaging reveals significant fibrosis and some right-sided bronchiectasis. Her muscle and skin disease are well managed with azathioprine 150mg daily and varying doses of prednisone (currently at 15 mg daily).

Are there any specific treatments for her dermatomyositis-associated interstitial lung disease that have been proven to be effective?

Key location(s): Right upper extremity **CASE 1**

Presented by Hal Weitzbuch, MD, MS and Warren Piette, MD

History of Present Illness

47 year-old African-American female with HIV/AIDS (last CD4 count 5 cells/µL) presented with a large, indurated, and tender right arm and an edematous right hand that had been worsening over 6 months. She had been seen the previous month by the dermatology inpatient service and a biopsy of her right arm for presumed lymphedematous Kaposi's sarcoma revealed florid cryptococcosis. She did not regularly take her antiretroviral or antifungal medications, and she left the hospital against medical advice. Additionally, she did not consistently attend her scheduled outpatient appointments. She had a history of intravenous drug abuse in both of her upper extremities. The patient was a resident of Chicago and denied any recent travel.

Past Medical History

HIV/AIDS (2000)
Chronic hepatitis C (2001)
Pneumocystis jiroveci pneumonia (2009)
Cervical intraepithelial neoplasia Grade 1 (2010)
Pulmonary aspergillosis (2010)
Cryptococcemia (2011)
Candidal esophagitis
Hypertension

Medications/Allergies

None/NKDA

Social History

Tobacco abuse (1/2 pack per day x 25 years)
IV heroin, smokes cocaine
No history of alcohol abuse

Review of Systems

The patient denied fever but described the following symptoms: occasional chills and night sweats twice per week, weight loss, shortness of breath, hemoptysis, and diarrhea

Physical Exam

Skin: Right mid-upper arm to the fingertips – fibrotic, indurated, tender, hyperpigmented and slightly violaceous plaque.
Soft Palate: Well-defined violaceous plaque

Laboratory Data

The following labs were remarkable/abnormal:

Hb/Hct	8.2 g/dL / 24.3%	[12.9 – 16.8 g/dL] / [38.1-49%]
WBC	1.6 k/µL	[4.4 – 10.6 k/µL]
Quantitative HIV RNA	40,640 copies/mL	
CD4 count	5 cells/µL	[590 – 1,060 cells/µL]

Histopathology
RIGHT UPPER ARM, PUNCH BIOPSY:
Kaposi sarcoma with tumor cells immunoreactive to human herpesvirus 8 (HHV-8) stain. Special stains for GMS, PAS, and mucicarmine confirmed the presence of *Cryptococcus neoformans*. Fite stain was non-contributory.

Microbiology
RIGHT FOREARM, TISSUE CULTURE:
Cryptococcus neoformans 2+ growth, AFB negative

Radiology
Chest radiograph: soft tissue mass in left upper lobe representing a mycetoma, unchanged from previous studies
CT right forearm: moderate, nonspecific, diffuse regional subcutaneous and deep soft tissue edema without subcutaneous emphysema; no loculated fluid collection; no evidence of osteomyelitis
Venous Doppler Ultrasound right arm: no deep vein thrombosis identified

Diagnosis
HIV/AIDS-associated Kaposi sarcoma with coexistent cryptococcosis in the same lesion, leading to an elective disarticulation

Treatment and Course
The patient was treated with intravenous amphotericin and one dose of daunorubicin as an inpatient. She was transitioned to oral voriconazole upon discharge. She was restarted on oral antiretrovirals but was noncompliant with her outpatient appointments. On readmission three months later, her right arm was only slightly improved. She consistently requested that the arm be removed because she felt it was cumbersome and nonfunctional. Ultimately, she underwent a right shoulder disarticulation at an outside hospital seven months after diagnosis.

Discussion
Human immunodeficiency virus affects 1.2 million Americans, with nearly 50,000 people contracting the virus annually. The most affected subpopulations in the United States are men who have sex with men (MSM), but black heterosexual women are the next highest group. Intravenous drug users are also a high-risk group.

Kaposi sarcoma (KS) in the setting of HIV infection is considered an AIDS-defining illness. KS is the most common neoplasm in people with AIDS and is induced by HHV-8, which can be found in lesions. Nnoruka et al. found that KS most often occurs when the total CD4 lymphocyte count drops below 200 cells/μL. The most common sites of cryptococcal infection are the lungs, central nervous system, and skin. These patients usually have a CD4 count of approximately 73 cells/ μL. Cutaneous cryptococcosis may be mistaken for KS as it can manifest as a cold cellulitis or a keloidal reaction. It can also be mistaken for an inflammatory pseudotumor. HHV-8 staining is helpful in differentiating KS from other malignant spindle cell tumors.

To date, twelve reports exist of KS coexisting with other infectious organisms. Associated organisms include *C. neoformans*, *Histoplasma capsulatum*, *Mycobacterium avium intracellulare* (MAC), *Mycobacterium gordonae*, *Mycobacterium tuberculosis*, *Candida albicans*, and one case with KS along with both *C. neoformans* and *MAC*. Although these findings may be coincidental in patients with poorly controlled AIDS, a causal association may apply. One explanation is that after *C. neoformans* infects the local tissue, various cytokines and oncotactic factors are released that stimulate KS growth. Alternatively, lesions of KS may be protective for

the yeast during episodes of cryptococcemia and allow growth despite systemic antifungal agents. A third view incorporates the ability of cryptococcal and KS lesions to form simultaneously in areas of local trauma, as in the Koebner phenomenon (e.g. KS in a dermatomal herpes zoster scar). Regardless of etiology, it is important for clinicians to be aware of the possibility of multiple diseases occurring in a single lesion in a patient with AIDS.

References

1. HIV in the United States: At A Glance. March 2012. (Accessed at http://www.cdc.gov/hiv/resources/factsheets/us.htm.)
2. Kemeny L, Gyulai R, Kiss M, Nagy F, Dobozy A. Kaposi's sarcoma-associated herpesvirus/human herpesvirus-8: a new virus in human pathology. Journal of the American Academy of Dermatology 1997;37(1):107-13.
3. Nnoruka EN, Chukwuka JC, Anisuiba B. Correlation of mucocutaneous manifestations of HIV/AIDS infection with CD4 counts and disease progression. International journal of dermatology 2007;46 Suppl 2:14-8.
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8. Ramdial PK, Sing Y, Subrayan S, Calonje E. Cutaneous colesional acquired immunodeficiency syndrome associated Kaposi sarcoma and cryptococcosis. The American Journal of dermatopathology 2010;32(8):780-6.
9. Niedt GW, Prioleau PG. Kaposi's sarcoma occurring in a dermatome previously involved by herpes zoster. Journal of the American Academy of Dermatology 1988;18(2 Pt 2):448-51.

Key location(s): Feet, ankles and right knee **CASE 2**

Presented by Julia Kasprzak, MD; Hal Weitzbuch, MD, MS; and Warren Piette, MD

History of Present Illness

58 year-old Puerto Rican male with HIV/AIDS (last CD4 count 184 cells/µL) presented with firm, painful nodules on his lower extremities for the past five years. They started on his feet and later appeared on his right knee. He was unable to wear his normal footwear due to the size and tenderness of the lesions.

At the time of presentation, he denied systemic symptoms such as fever, chills, nausea, vomiting, weight loss, cough, or night sweats.

Past Medical History

HIV/AIDS– diagnosed in 2007 and lost to follow-up until June 2011, when he presented again at the HIV Core clinic and was started on antiretroviral therapy
History of syphilis, treated in 2007

Medications

Shortly before presentation to our clinic, he was started on antiretroviral therapy with emtricitabine/tenofovir/efavirenz. He was also taking daily fluconazole and TMP-sulfa.

Allergies

PCN – rash

Social History

The patient was born and raised in Puerto Rico. He had a long history of alcohol and IV-drug use. At the time of presentation, he was living in a drug rehabilitation facility and did not have contact with his family.

Physical Exam

Vitals: Normal
Skin: Feet, ankles, right knee with red-brown to violaceous, firm dome-shaped nodules, tender to palpation

Laboratory Data

The following labs were remarkable/abnormal:

Cr	1.6 mg/dL	[o.6 – 1.4 g/dL]
BUN	26 mg/dL	[8 – 20 g/dL]
Albumin	2.4 g/dL	[3.8 – 5.2 g/dL]
ALT	71 U/L	[5 – 35 U/L]
Hb/Hct	10.2 g/dL / 29.6%	[12.9 – 16.8 g/dL] / [38.1 – 49%]
MCV	104.5 fL	[81.9 – 92.8 fL]
Platelets	89 k/µL	[161 – 369 k/µL]
CD4 count	184 cells/µL	[590 – 1,060 cells/µL]

The following labs were unremarkable/negative:
Na, K, Cl, HCO3, glucose, AST/ALT, hepatitis B serologies, hepatitis C antibody, urine Histoplasma Ag, urine cryptococcal Ag

Histopathology

RIGHT KNEE, PUNCH BIOPSY:
Dermis with acute and chronic inflammation including numerous neutrophils and eosinophils along with chronic onion-skin fibrosis around the vessels. PAS, GMS, and AFB stains were negative for fungus and acid fast bacilli.

Diagnosis

Erythema elevatum diutinum (EED) in the setting of HIV/AIDS

Treatment and Course

The patient was started on dapsone 25 mg daily. The plan was to increase the dose at a monthly follow-up appointment. Unfortunately, he never returned to the dermatology clinic for follow-up.

Discussion

EED is a rare vasculitic process, which presents in middle-aged to older adults. Lesions usually occur in a symmetric, periarticular, and acral distribution. Early in the course of the disease, they present as soft, purpuric macules or papules. These later coalesce into plaques that later turn into red-brown to violaceous firmer plaques, papules, or nodules. Nodular, bulky lesions like those in our patient are unusual and have been described mostly with HIV infection. Histologically, EED presents as leukocytoclastic vasculitis and capillary proliferation with progression to significant fibrosis in late lesions. Older lesions can also contain lipid deposits.

The pathogenesis of vasculitis in EED is unknown. It may be caused by endothelial immune complex deposition in response to viral or bacterial antigens. It has been linked to autoimmune processes including Crohn disease, celiac disease, relapsing polychondritis, and rheumatoid arthritis; hematologic diseases including myelodysplasia, multiple myeloma, lymphoma, and IgA paraproteinemia; and infectious diseases including strep infection, viral hepatitis, syphilis, and HIV infection. Some cases have no apparent related disorders.

EED is known to be associated with HIV-1 infection and it occasionally may be a presenting sign of HIV. Therefore, it is important to not only test those who present with EED for HIV/AIDS, but also to always keep EED in the differential diagnosis of skin lesions affecting patients with HIV/AIDS. Other conditions may mimic EED clinically and histologically including urticarial vasculitis, sclerosing hemangioma, fibrous histiocytoma, and Kaposi sarcoma. In the setting of HIV, an HHV-8 stain may be useful to distinguish Kaposi sarcoma and EED, but it is not routinely required.

EED follows a chronic course and treatment is limited. Some patients can experience spontaneous resolution after 5-10 years, while other cases have been reported of lesions persisting for more than 39 years. In some case reports, dapsone at 100 mg daily has shown to provide some benefit in resolution of skin lesions.

References

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2. Martin JI, Dronda F, Chaves F. Erythema elevatum diutinum, a clinical entity to be considered in patients infected with HIV-1. Clinical and experimental dermatology 2001;26(8):725-6.
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Key location(s): Lower extremities **CASE 3**

Presented by Stephanie St. Pierre, MD; Morayo Adisa, MD; and Warren Piette, MD

History of Present Illness

54 year-old African-American female presented to the dermatology clinic complaining of a one-week history of red lesions and small blisters on the legs. The lesions were pruritic and painful. She also noted a progressive increase in swelling of the legs and ankles. Two days prior to the onset, she experienced generalized aching, joint pains, chills, and malaise, which resolved without fever within one day. The patient reported three similar episodes of chills and malaise over the preceding year. Her pain was relieved with naproxen and gabapentin. She was biopsied and given a presumptive diagnosis of immune-complex vasculitis with secondary bullae.

Two days after her initial presentation, she was admitted to the internal medicine service for pain control related to widespread bullae that had developed on the lower extremities. In addition, purpuric macules had also appeared on the abdomen and posterior arms.

Past Medical History

Diabetes mellitus type II, peripheral neuropathy, hypertension, cervical cancer s/p hysterectomy two years ago, two early miscarriages

Medications

Gabapentin, insulin, enalapril, naproxen, lovastatin, aspirin, hydrochlorothiazide

Allergies

PCN – rash in childhood

Review of Systems

Denied the following: headaches, sore throat, eye pain/ulcerations, fever, cough, chest pain, SOB, diarrhea, bloody stools, abdominal pain, dysuria, hematuria, focal weakness, no mouth/anogenital lesions, or hair loss

Physical Exam

Initial presentation
Legs and feet: round purpuric macules with dusky centers, some of with small vesicles centrally
Knees: few red macules
Left medial leg: one decompressed bulla

Day of admission (2 days later)
Lateral arms, abdomen, legs/feet: purpuric macules
Legs: widespread tense non-hemorrhagic bullae, some on a purpuric base

Laboratory Data

The following labs were remarkable/abnormal:

ANA	homogeneous pattern, >1:160	[<1:160]
Anti-dsDNA Ab	1.44 U	[Positive ≥1.10 U]
Urinalysis	glucose 150, protein 10, WBC 161, small blood with RBC 19, squamous epithelial cells 11	
RPR Quantitative Titer	1:128	[Negative]
PPA	Reactive	

The following were unremarkable/negative:
CMP, CBC with differential, HIV 1/2 antibody, Quantitative HIV RNA, Hepatitis B surface Ag/Ab and core Ab, Hepatitis C Ab, Rheumatoid Factor, C3, C4, cryoglobulins, GC/Chlamydia PCR, p-ANCA, c-ANCA, anti-Smith Ab, anti-Ribonucleoprotein, anti-Smith Ab, anti-SSA Ab, anti-SSB Ab, anti-centromere Ab, lupus anticoagulant, anti-B2 glycoprotein, anti-cardiolipin Ab

Histopathology
LEFT ANTERIOR LEG, PUNCH BIOPSY:
Perivascular interstitial infiltrate consisting of neutrophils and nuclear dust. Extravasated erythrocytes evident. Small focal DEJ separation noted in background of papillary dermal edema. DIF was negative for immunostaining; IHC stain for treponemes was negative.

Diagnosis
Bullous cutaneous small-vessel vasculitis in the setting of secondary syphilis

Treatment and Course
Upon initial admission, the patient was treated with high dose prednisone and pain medication with improvement of symptoms over three days. On the last day of admission, an RPR was ordered and noted to be positive upon follow-up in the dermatology clinic. In conjunction with the infectious diseases service, the patient was diagnosed with secondary syphilis or, alternatively, early latent syphilis with recurrence. Given her allergy to penicillin, was started on a one month course of doxycycline 100mg BID. She was also treated for Trichomonas vaginitis at that time.

Two weeks after initial presentation, she was again admitted for management of severe burning leg pain, and a rheumatology consult was obtained. The pain was attributed to mononeuritis multiplex in the setting of vasculitis. She was restarted on prednisone while simultaneously continuing doxycycline for treatment of syphilis. Of note, the bullous lesions on the legs had begun to regress at this time and the RPR titer had decreased from 1:128 to 1:64. Ultimately, she completed 4 weeks of doxycycline in addition to prednisone up to 20-40 mg daily with subsequent taper. She did not have recurrence of purpura or bullae. Her RPR continued to trend down and reached a titer of 1:16 at two months after initiation of treatment.

Discussion
Secondary syphilis, which can present in many ways, is historically considered the "great imitator." After the initial chancre of primary inoculation has appeared, hematogenous spread of bacteria can lead to widespread cutaneous manifestations within 6-8 weeks. Early on, a roseola-like macular eruption may be seen on the upper body, and later may generalize. However, the generalized papulosquamous eruption is more common. Other skin findings may include annular or figurate plaques with hyperpigmented centers or granulomatous nodules and plaques, and localized syphilids on the palms/soles, in the anogenital area (condyloma lata), and in a seborrheic distribution. The mucosal surfaces may demonstrate perlèche, aphthous ulcers, sore throat, and mucous patches. Patchy moth-eaten alopecia or telogen effluvium may also be effects of syphilitic infection.

Cutaneous small-vessel leukocytoclastic vasculitis (LCV) associated with syphilis is rare, and an associated bullous form has not been previously described in the literature. Cam et al. reported a newborn diagnosed with congenital syphilis presenting with papulopurpuric and hemorrhagic vesicular eruption on the extremities that was found to be LCV on biopsy. Kim et al. described a case of an HIV-negative Korean man with multiple penile ulcers that demonstrated LCV on skin biopsy. The lesions did not improve with colchicine and systemic corticosteroids, and only after repeated testing did the VDRL turn positive. Furlan et al. reported an HIV-positive male who

presented with evanescent, pink macules on the back that were found on biopsy to be consistent with LCV. His serologic tests later showed infection with syphilis.

Our patient demonstrated a highly elevated RPR with a positive confirmatory treponemal test, but her skin eruption was not typical for secondary syphilis. Further confounding the clinical picture were positive ANA and dsDNA serologies which suggested a possible underlying diagnosis of SLE, however, the patient did not fulfill any other SLE criteria. Of additional interest is her clinical picture which was distinctive in that only some of the bullae were on a purpuric base, and all of the bullae were clear (non-hemorrhagic). This is notable because the mechanism of bullae formation is thought to be ischemic, with necrosis and vascular hemorrhage.

The patient responded well to doxycycline therapy with improvement of her skin lesions and an appropriate decrease in RPR titers. We present this case to highlight yet another unusual presentation of secondary syphilis.

References

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Unknown A

What is the unifying diagnosis?

Please place your answer in the ballot box.

Unknown B

What is the unifying diagnosis?

Please place your answer in the ballot box.

Key location(s): Nose **CASE 4**

Presented by Elizabeth Fahrenbach, MD and Warren Piette, MD

History of Present Illness
34 year-old Hispanic male presented with friable, ulcerated plaques on the right nasal ala and nares. He first noticed a papule on the right nasal ala 1.5 years ago and associated it with a soccer injury. Over time, it progressively enlarged and ulcerated.

The patient was originally from Ecuador and had no history of travel outside of the Chicago area since emigrating 3 years ago. His path of emigration took him from Ecuador to Northern Mexico, where he spent a few weeks before continuing to Chicago.

Past Medical History
Primary syphilis, treated 10 years ago

Medications/Allergies
None/NKDA

Social History
No tobacco, alcohol or illicit drug abuse. Works as a furniture mover. His wife and two children live in Ecuador. History of sex with prostitutes in Ecuador over three years ago.

Review of Systems
The patient had mild cough, occasional difficulty breathing through the nose, and occasional dull headaches. He denied fevers, chills, dyspnea, night sweats, and weight loss.

Physical Exam
Lymph: No cervical lymphadenopathy
Skin: Right nasal ala and bilateral nares with friable, ulcerated plaques

Laboratory Data
The following labs were remarkable/abnormal in January 2011:

RPR Quantitative Titer	1:4	[Negative]
PPA	Reactive	
HIV 1/2 antibody	Positive	[Negative]
CD4 count	175 cells/μL	[590 – 1,060 cells/μL]

Lumbar puncture in January 2011:

Fluid color	Clear	
Glucose	42 mg/dL	[50 – 70 mg/dL]
Protein	110 mg/dL	[20 – 50 mg/dL]
WBC	102/μL	[0 – 5/μL]
RBC	36/μL	
PMNs	10%	[0 – 6%]
Lymphocytes	89%	[40 – 80%]
Monocytes	1%	[15 – 45%]

January 2012:

CD4 count	250 cells/μL	[590 – 1,060 cells/μL]

Histopathology
RIGHT NASAL ALA, PUNCH BIOPSY:
A tangentially oriented specimen showing acute and chronic inflammation with microabscess formation. No microorganisms seen on AFB, PAS or silver (GMS, reticulin) stains.

Radiology
Chest Radiograph (January 2011): right upper lung with linear fibrocystic opacities and interstitial densities
CT head with and without contrast (January 2011): likely arachnoid cyst in the left posterior fossa; mucosal thickening is noted in the ethmoidal and maxillary sinuses representing an ethmoidal sinusitis, otherwise normal
CT head with and without contrast (January 2012): arachnoid cyst in the posterior cranial fossa is still present, otherwise normal

Microbiology
RIGHT NASAL ALA, TISSUE CULTURE:
1+ growth of dimorphic fungi. *Coccidioides immitis/posadasii* confirmed by DNA probe.

CEREBROSPINAL FLUID CULTURE:
January 2011: no growth
January 2012: *C. immitis/posadasii* confirmed by DNA probe

Diagnosis
Disseminated coccidioidomycosis in the setting of HIV/AIDS

Treatment and Course
After biopsies were taken for histological review and tissue culture, the patient was referred to the infectious disease specialist who initiated HAART for treatment of HIV/AIDS. At a follow-up appointment he complained of worsening severity of headaches and cough. He was admitted to the hospital and a chest radiograph, lumbar puncture, and head CT were done. The findings on lumbar puncture were consistent with fungal meningitis. Culture of the CSF yielded no growth, but tissue culture from the right nasal ala revealed dimorphic fungi, confirmed to be coccidioidomycosis by DNA probe. Intravenous amphotericin B was initiated for treatment of coccidioidal meningitis with likely dissemination from the lung. The patient gradually showed improvement in his symptoms and amphotericin B was replaced with long-term oral fluconazole therapy. In follow-up dermatology visits, the patient exhibited impressive resolution of the plaques on the nose with no functional defects and minimal cosmetic deformity.

The patient continued on HAART and fluconazole for a year with no issues. However, in late December 2011, he discontinued fluconazole due to poor access to medications. In early January 2012, he presented to his infectious disease provider with severe headaches, meningismus, fevers, and vomiting. He was admitted to the hospital and lumbar puncture and head CT were repeated. Culture of the CSF grew *C. immitis*, which was treated with intravenous and later oral fluconazole. The patient recovered from the second episode of coccidioidal meningitis with no functional neurologic deficit. He will require life-long fluconazole therapy.

Discussion
Coccidioidomycosis (also known as San Joaquin Valley Fever) is an endemic fungal infection found in the lower Sonoran desert ecozone of the Western hemisphere (including west Texas, Arizona, New Mexico, parts of central America, Argentina, northwest Mexico, and the San Joaquin Valley in California). The fungus produces arthroconidia in the soil. It thrives during rainy summer seasons, followed by dry winters with windstorms to disperse the air-borne spores.

Construction, archeological excavations, military exercises, as well as natural causes of disruption to the topsoil can incite epidemics, as evidenced by the 1994 earthquakes in Ventura County, California.

In 2002, two morphologically identical species of Coccidioides were recognized: *C. immitis and C. posadasii*. The two species can be distinguished by variations in growth rate and genetic analysis. *C. posadasii* grows more slowly and is found in the deserts of southwestern USA, Mexico, and South America. *C. immitis* grows more rapidly and is primarily found in the San Joaquin Valley region in California as well as in the southwestern USA and Mexico.

While *Coccidioides spp*. can infect individuals with normal immune function, immunocompromised patients are particularly susceptible, especially patients with HIV. In a prospective study done in Arizona, 25% of HIV patients developed coccidioidomycosis over a 3.5 year period. The major risk for development of progressive coccidioidomycosis is a CD4 count less than 250 cells/µL, regardless of length of residency in an endemic area. Other recognized factors conferring an increased risk of infection are pregnancy, male gender, Filipino ancestry, treatment with TNF alpha inhibitors, old age, and blood types AB and B. The later suggests a possible genetic predisposition.

The route of infection in the vast majority of cases is through the respiratory tract. Most respiratory infections are asymptomatic, or only display mild symptoms such as fever and cough. Coccidioidomycosis may affect the skin in multiple ways. Reactive lesions where organisms are not expected to be identified in the skin are erythema nodosum, acute exanthema, erythema multiforme-like eruptions, Sweet's syndrome and interstitial granulomatous dermatitis. Reactive lesions may be seen in 15% of men and 30% of women with primary pulmonary disease.

Skin lesions with identifiable organisms are seen in primary cutaneous coccidioidomycosis and disseminated cutaneous coccidioidomycosis. Primary cutaneous infection is very rare and is usually due to traumatic inoculation in laboratory or farm workers in endemic areas. Extrapulmonary dissemination is also rare (<1% of cases) and the most common organ affected is the skin. Other organs commonly involved by disseminated coccidioidomycosis are the bones, joints, eyes and the central nervous system. While coccidioidal meningitis affects only 1% of hosts with normal immunity, it is much more common in HIV positive patients, affecting 14 of 91 patients in a study performed in an endemic area. Current recommendations are for life-long fluconazole therapy for patients diagnosed with coccidioidomycosis in the setting of HIV, largely in part to the risk of coccidioidal meningitis. Coccidioidal meningitis is commonly complicated by stroke and hydrocephalus and has a mortality rate of 40%.

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Key location(s): Trunk, extremities, acral surfaces, scalp **CASE 5**

Presented by August A. Natalie, MD and Warren Piette, MD

History of Present Illness

21 year-old African-American female presented to the emergency department in February 2011 with a three-week history of worsening of her chronic skin disease and generalized pruritus. This was associated with subjective fevers, night sweats, and generalized myalgias. She was admitted to the internal medicine service.

Her skin disease began twenty-four months prior to admission. Twenty months prior to admission, she was first seen in outpatient dermatology clinic for generalized skin-colored, monomorphic papules on the extremities and trunk associated with considerable pruritus. A working diagnosis of follicular-type atopic dermatitis was made. Over the next four months, she was treated unsuccessfully with topical corticosteroids, intramuscular triamcinolone, and varying doses of oral prednisone. Sixteen months prior to admission, she developed nonscarring, patchy occipital and vertex scalp hair loss. Blood work revealed an absolute eosinophil count of 1,100 cells per microliter. She was started on mycophenolate mofetil, which was quickly increased to 3g/day. Her skin and hair disease and pruritus progressed on this regimen. She began wearing a hair prosthesis. She failed oral hydroxyzine, doxepin, gabapentin, and mirtazapine for her pruritus. Fourteen months prior to admission, two skin biopsies revealed superficial perivascular dermatitis with lymphocytes and eosinophils and focal lymphocytic exocytosis. Eleven months prior to admission, the absolute eosinophil count was 1,400 cells per microliter. The mycophenolate mofetil was stopped nine months prior to admission because of continued cutaneous progression and an episode of lower extremity thrombophlebitis. Eight months prior to admission, she developed palmoplantar painful keratoderma and left inguinal lymphadenopathy in conjunction with her skin and hair disease. Cyclosporine, oral methotrexate, and varying doses of oral prednisone were initiated. Six months prior to admission, she began noting intermittent episodes of dyspnea that would awaken her in the middle of the night and persistent lower extremity edema. She had gained 100 pounds of weight compared to her baseline in 2009.

Four months prior to admission, she was noted to have significant resting sinus tachycardia (120s -130s and normal TFTs). She was admitted to the hospital briefly for intravenous fluids, intravenous antibiotics, and an increase in oral prednisone. Psychiatry was consulted while inpatient. She was diagnosed with an adjustment disorder with depressed mood and post-traumatic stress disorder all stemming from her lack of control over her disease and symptoms. Two months prior to admission, she was again admitted to the hospital because of significant orthopnea, tachycardia, and recalcitrant skin disease and pruritus. She was given intravenous fluids and pulse-dose intravenous methylprednisolone. A computed tomography scan of the chest/abdomen/pelvis was performed and another skin biopsy was taken. The absolute eosinophil count two months prior to admission was 1,700 cells per microliter. She had no other significant past medical history. She lived with her mother and was attending school. There was no significant travel history.

At the time of admission, she noted anorexia, nausea, vomiting, tingling in the distal extremities, lower extremity weakness, suprapubic pain, and urinary frequency with urgency. She had a productive cough with yellow sputum, increased nocturnal and exertional dyspnea, and significant orthopnea that required her to sleep upright in a chair. Her exercise tolerance was limited to walking “half a block”.

Outpatient Medications at Time of Admission

Prednisone 20mg PO Daily, cyclosporine 100mg PO Q12H, methotrexate 17.5mg PO QWeekly, triamcinolone 0.1% ointment, clobetasol 0.05% ointment, hydrophilic ointment, hydroxyzine, diphenhydramine, folic acid, pantoprazole, hydrochlorothiazide, albuterol inhaler

Physical Exam

Vitals: 99.0ºF, 134 bpm, 145/93 mm Hg, 18 bpm, 94% on room air, BMI 50
Gen: Obese, no acute distress, alert and oriented x 3, depressed mood, anxious
CV: Tachycardia, regular rhythm, normal S1 and S2; S4 gallop present; **pansystolic murmur in mitral valve area;** JVD present
Pulm: Bilateral basilar crackles
Abd: No hepatosplenomegaly
Lymph: No cervical, supraclavicular, axillary, or inguinal lymphadenopathy
Ext: 1+ edema of the lower extremities
Skin: Fine, skin-colored papules with lichenification over nearly the entire skin surface, including the forehead, chest, back, abdomen, and extremities; keratoderma of palms and soles; faint background erythema on the lower legs; shins consistent with lichen amyloidosis

Laboratory Data

The following initial labs were remarkable/abnormal:

Phosphorus	5.0 mg/dL	[2.5 – 4.5 mg/dL]
Uric Acid	8.2 mg/dL	[3.0 – 7.0 mg/dL]
LDH	506 U/L	[85 – 210 U/L]
WBC	22.3 k/µL	[4.4 – 10.6 k/µL]
Absolute lymphocyte count	6800/µL	[1200 – 3400/µL]
Absolute eosinophil count	1900/µL	[0 – 400/µL]

Urinalysis: loaded WBC, many bacteria

The following labs were unremarkable/negative:
TFTs, HIV, plasma metanephrine, plasma normetanephrine

Radiology

CT abdomen/pelvis w/o contrast (12/2010): normal liver and spleen, no retroperitoneal or pelvic adenopathy
CT chest w/ and w/o contrast (2/2011): **nodular, patchy, bilateral lower lobe confluent foci of ground glass opacities**; bilateral benign axillary nodes; no hilar adenopathy, normal heart size and pericardium

Transesophageal Echocardiogram (2/2011)

Dilated left ventricle to 6.2 cm with bilateral atrial enlargement; left ventricular ejection fraction 40% with diffuse hypokinesis and no wall motion abnormalities; **severe 4+ mitral regurgitation**; **mitral valve with significant restriction of posterior leaflet and thickening of the anterior leaflet**; no evidence of flail; mild aortic valve regurgitation; estimated pulmonary artery pressure 60 mmHg

Peripheral Flow Cytometry (2/2011)

T Lineage		B Lineage		Myeloid Lineage		Activation Antigens	
CD2	96%	CD19	4%	CD14	<1%	CD38	2%
CD3	**11%**	CD19Kap	2%	CD15	2%	HLA-DR	69%
CD4	**10%**	CD19Lamb	1%	CD33	<1%		
CD5	96%	CD20	3%	CD34	<1%		
CD7	32%	CD20Kap	2%	MP	<1%		
CD8	**88%**	CD20Lamb	1%				
CD16	8%	CD19CD5	1%				
CD56%	44%	CD19CD10	<1%				
cytoCD3	84%	TDT	<1%				

An abnormal T cell population was detected which showed expression of surface CD2, CD5, and cytoplasmic CD3 with loss of surface CD3 and partial loss of CD7. A portion of the population shows CD56 expression. This population is negative for TDT and CD34. The CD4:CD8 ratio was 1:9. Review of the blood smear showed lymphocytosis composed of small and intermediate-sized lymphoid cells, many of which contain highly irregular nuclei. Atypical lymphocytes number 7% of smear.

Right Posterior Iliac Crest Bone Marrow Biopsy and Aspirate (2/2011)

The marrow showed 50-60% cellularity with trilineage hematopoiesis and normal maturation. Interstitial highly atypical lymphoid cells with irregular nuclei were identified. There was an increase in eosinophils. **FISH studies were negative for FIP1L1-PDGFRA, -PDGFRB, and -FGFR1.** Flow cytometry of the bone marrow aspirate revealed that the abnormal clone was identical to the peripheral blood clone, and it occupied 30% of the bone marrow aspirate.

Bronchoscopy with Bronchoalveolar Lavage (2/2011)

Normal pharynx, larynx, trachea, left and right bronchial tree was present. Right middle lobe bronchoalveolar lavage fluid was negative for malignant cells and organisms (including ova/parasites). 2% eosinophils were present on the BAL fluid.

Histopathology

1. TRANSBRONCHIAL BIOPSY OF RIGHT LATERAL BASAL SEGMENT (2/2011)

Congested hemorrhagic lung parenchyma with focal type 2 pneumocyte hyperplasia and foci of acute inflammatory exudate and fibrin deposits, suggestive of pneumonia. There was no evidence of a lymphoproliferative disorder. Acid fast and fungal stains were negative.

2. LEFT UPPER ARM, PUNCH BIOPSIES (12/2010):

Sections display a moderately dense superficial dermal perivascular inflammatory infiltrate underlying a mildly acanthotic epidermis. In several sections, there are intraepidermal collections of atypical mononuclear cells. Several of the atypical intraepidermal cells display cerebriform nuclei. The inflammatory cells are CD3 positive. The CD4:CD8 ratio is approximately 1:1. Scattered atypical intraepidermal mononuclear cells are positive for CD8 and CD4. CD56 is negative. The T cell gene rearrangement (gamma chain, PCR) of the skin biopsy showed a monoclonal band.

Diagnosis

Hypereosinophilic syndrome, T-lymphocytic variant (L-HES), with cutaneous, pulmonary, and cardiac involvement

Treatment and Course

Upon admission, the dermatology service recommended a peripheral blood flow cytometry study, which revealed the $CD3^-CD4^-CD8^+$ clone. Infectious diseases, hematology, pulmonology, and cardiology were consulted. An infectious etiology for the pulmonary findings was ruled out. Her cardiac and pulmonary symptoms were due to congestive heart failure, which was secondary to severe mitral regurgitation. Her heart failure was managed by the cardiology and primary service. Her cardiopulmonary symptoms vastly improved after one week of medical therapy. Cardiothoracic surgery was consulted regarding their opinion on an elective mitral valve replacement. Since she had improved with medical therapy, close outpatient follow-up with a repeat echocardiogram was planned. Her skin disease and heart disease was managed with oral prednisone 1mg/kg daily. She was discharged on prednisone 100 mg daily with close outpatient follow-up. Her skin biopsy was sent to the Cleveland Clinic. They felt that the skin biopsy was consistent with a $CD8^+$ Sézary syndrome.

As an outpatient, low dose subcutaneous alemtuzumab (anti-CD52) was initiated. The plan was for 6 weeks of 15mg SC. The dose was increased to 30mg on week 6 because of continued pruritus, and she received a seventh week of 30mg SC. TMP/SMX, acyclovir and fluconazole were provided for prophylaxis. She was able to wean completely off prednisone at the end of the first alemtuzumab cycle. Two months after the initial alemtuzumab cycle, a peripheral flow cytometry was unable to identify an abnormal circulating lymphocyte population. The CD4:CD8 ratio was 5:1. Her pruritus persisted and the eosinophil count rebounded, so three months after the last dose of alemtuzumab, she was started on a second cycle of 30mg SC thrice weekly for 6 weeks. Three months after the second cycle, a peripheral flow cytometry showed no evidence of clonality (the CD4:CD8 ratio was 1.5:1). However, the eosinophils have risen to 500cells/μL. Four months after the second dose, she has undergone HLA typing. If she relapses, allogeneic hematopoietic stem cell transplantation will be considered.

Discussion

The hypereosinophilic syndromes (HES) are a group of disorders marked by sustained overproduction of eosinophils, in which eosinophilic infiltration and mediator release cause damage to multiple organs. HES is rare and the true prevalence unknown. Most patients are diagnosed between the ages of 20 and 50. HES is subdivided into several variants: myeloproliferative variants of HES, L-HES, familial HES, undefined HES, overlap HES, and associated HES.

L-HES is more insidious in nature and is characterized by a predominance of skin and soft tissue involvement. In this variant, IL-5 producing T cell subsets have been identified in the peripheral blood. The most frequently reported abnormal T cell phenotype in L-HES is $CD3^-CD4^+$. In a number of patients, especially in early clinical stages, the T cell clone may escape detection. The diagnosis can be supported by an increased IgE level, hypergammaglobulinemia, and elevated serum levels of TARC (thymus and activation-regulated chemokine). The prevalence of L-HES is not well defined. In one small study, L-HES represented 27% of all HES.

L-HES is associated with severe pruritus, eczema, erythroderma, urticaria, and angioedema, as well as lymphadenopathy, and endomyocardial involvement.

When combining all HES subtypes, the organ systems most frequently involved at presentation are dermatologic (37%), pulmonary (25%), gastrointestinal (14%), and cardiac (5%). Pulmonary disease classically presents with dyspnea or cough, and the most common infiltrate pattern on imaging is a patchy ground glass pattern, which was present in our patient. Cardiac abnormalities in L-HES occur less commonly than in myeloproliferative HES. Cardiac disease progresses to a restrictive cardiomyopathy and/or mitral valve regurgitation due to entrapment

of the chordae tendineae, which was seen in our patient. Endomyocardial biopsy provides definitive evidence of eosinophil associated cardiac involvement, but is typically only reserved for patients in whom there is uncertainty. Eosinophilic cardiomyopathy is the most common cause of death associated with HES. Peripheral neuropathy accounts for one-half of the neurologic manifestations. Our patient noted distal tingling sensation in all extremities on admission, but this issue has since resolved.

The dermatologic manifestations of HES are protean. The reported signs include angioedema, eczema, erosions, erythema, erythema annulare centrifugum, erythroderma, excoriations, livedo reticularis, macules, mucosal (oral and genital) ulcers, nail fold infarcts, necrotizing vasculitis, nodules, papules, patches, pruritus, purpuric papules, splinter hemorrhages, ulcers, urticaria, vasculitis, and Well's syndrome. Urticaria and angioedema occur in all HES subtypes and are characteristic of certain subtypes (i.e. episodic angioedema with eosinophilia). Histology of HES demonstrates a superficial and deep perivascular mixed inflammatory cell infiltrate of eosinophils and lymphocytes. Flame figures are typically not seen. Cutaneous microthrombi may be present, but their presence portends a poor prognosis.

End-organ involvement may develop insidiously and is not correlated with the degree of blood eosinophilia. Therefore, all patients, including those who are asymptomatic, should undergo screening for organ involvement at six-month intervals. This includes hepatic enzymes, renal function, troponin, EKG, ECHO, and PFTs. One quarter will develop a thrombotic complication. Early HLA typing should be considered.

For FIP1L/PDGFRA-negative HES, therapy is indicated for symptomatic patients or those with evidence of developing end-organ damage. Glucocorticoids are the initial therapy of choice, usually at doses of 1mg/kg daily for at least 1 to 2 weeks. Strongyloides infection should be excluded prior to initiation of glucocorticoids. Once tapered down to a lower dose of steroid, steroid-sparing agents can be added. Commonly used steroid sparing agents include hydroxyurea, interferon alfa, mepolizumab (anti-IL-5), alemtuzumab (anti-CD52). Less frequently used options include cladribine, chlorambucil, vincristine, methotrexate, cyclosporine, cytarabine, cyclophosphamide, and etoposide.

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Key location(s): Face, upper extremities, trunk, lower extremities **Case 6**

Presented by Mona Gandhi, MD and Warren Piette, MD

History of Present Illness

48 year-old male presented with a seven-month history of a generalized, mildly pruritic, erythematous, scaly eruption. In addition, he reported intermittent fevers, joint pains, diffuse hair loss over his arms, legs, and scalp, and a thirty-five pound weight loss. Notably, he was recently diagnosed with anterior uveitis and had been started on oral prednisone per the ophthalmology service.

Past Medical History

Diabetes Mellitus II
Gastroesophageal reflux disease

Medications/Allergies

Prednisone, glipizide, atropine eye drops, prednisone eye drops, pantoprazole
NKDA

Physical Exam

Vitals: T 98°F, HR 82 bpm, BP 105/68
General: Alert and oriented, eyes with conjunctival injection
Lymph: Cervical and axillary lymphadenopathy, less than one centimeter
Skin: Erythrodermic
Face, upper extremities, torso, and lower extremities: erythema and focal areas of desquamation; palms and soles with few hyperkeratotic plaques
Fingernails: irregular pitting

Laboratory Data

The following labs were remarkable/abnormal:

WBC	**73.3 K/µL**	**[4.4 – 10.6 K/µL]**
Neutrophil %	15.8 %	[45.3 – 74.5 %]
Lymphocyte %	81.9%	[18.1 – 43.2 %]
Eosinophil %	0.1%	[0.4 – 5.8 %]
LDH	402 U/L	[85 – 210 U/L]

The following labs were unremarkable/normal:
CMP, HIV 1/2 antibody, RPR

Right Posterior Iliac Crest Bone Marrow Biopsy and Aspirate

Cellularity of approximately 50%. There is an interstitial infiltration of the marrow by small lymphoid cells.

Karyotype

An abnormal male karyotype with multiple chromosome abnormalities:
45,XY,-1,der(4)t(1;14)(q21;q21),der(9)t(1;9)(p22;p22),der(9)t(4;9)(q21;p13),add(19)

Peripheral Blood Smear and Flow Cytometry
Peripheral blood smear showed leukocytosis composed of mature, small-medium sized lymphoid cells with irregular nuclei. Flow cytometry studies performed on peripheral blood show an abnormal T-cell population which showed co-expression of CD2, CD3, CD4, CD5, and CD52 but was negative for CD7, CD8, CD25, CD34, and TDT.

Histopathology
LEFT UPPER ABDOMEN, PUNCH BIOPSY:
Sparse superficial perivascular lymphocytic infiltrate. There were lymphocytes at the dermal-epidermal junction and focal areas of exocytosis.

Radiology
CT chest, abdomen, and pelvis: enlarged bilateral axillary lymph nodes; no mediastinal or hilar lymphadenopathy

Diagnosis
Sézary syndrome (T4NxM1B2, Stage IVB) with anterior uveitis (most likely secondary to the leukemia)

Treatment and Course
The patient was admitted to the inpatient hematology-oncology service and started on a twelve-week course of alemtuzumab, a monoclonal antibody targeting CD52. The initial dose was given as an infusion and subsequent doses were given subcutaneously, 30 mg thrice weekly in an outpatient infusion center. By week three, the patient had near complete resolution of skin symptoms and the WBC count decreased to 10.7 K/μL with 22.1% lymphocytes. In addition, the anterior uveitis was resolving and his intraocular pressures were found to be normal per ophthalmology.

Discussion
Sézary syndrome (SS) and mycosis fungoides (MF) are the most common forms of cutaneous T-cell lymphomas (CTCL). According to recent data from the US National Cancer Institute's Surveillance, Epidemiology, and End Results, SS accounted for 2.5% of the reported CTCL cases from 1973-2002; MF accounted for 72%.

SS and MF are closely related, but new evidence regarding their molecular profiles suggests that they are distinct entities. It was recently demonstrated that clonal malignant T-cells from blood of leukemic variants of CTCL patients co-express the lymph node homing molecule CCR7 and L-selectin, in addition to the central memory cell marker CD27. In contrast, T-cells from MF skin lesions are negative for CCR7/L-selectin and CD27, but strongly express skin resident effector memory T-cell markers CCR4 and CLA. This suggests that SS is a central memory T-cell neoplasm, while MF is a malignancy of skin resident effector memory T-cells. This distinction is important in regard to both T-cell biology and therapeutics.

The clinical features of SS include the classic triad of erythroderma (>80% body surface area), lymphadenopathy, and the presence of greater than five percent malignant T-cells with cerebriform nuclei (Sézary cells). Flow cytometric analysis confirms the diagnosis. Other skin manifestations include pruritus, palmoplantar keratoderma, alopecia, and nail dystrophy. Ocular findings can be seen with advanced disease. The most common eye findings seen in CTCL include cicatricial eyelid ectropion, blepharoconjunctivitis, and eyelid edema and thickening. Our patient presented with anterior uveitis, which has been reported in association with various T cell leukemias/lymphomas, but to our knowledge not specifically with Sézary syndrome.

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Unknown C

What is the unifying diagnosis?

Please place your answer in the ballot box.

Key Location(s): Scalp, eyebrows, eyelashes, axillae, groin **CASE 7**

Presented by Sumul Gandhi, MD; August A. Natalie, MD; and Jerry Feldman, MD

History of Present Illness

48 year-old African-American female presented to our clinic with a four-month history of hair loss affecting the scalp, eyebrows, eyelashes, axillae, and pubic area. The hair had been falling out in patches "from the base" without any associated symptoms. She denied any recent stressors or change in lifestyle.

Past Medical History

Severe symptomatic iron deficiency anemia without known source (Hgb as low as 5 g/dl in 2007, EGD normal, colonoscopy declined)

Medications/Allergies

Methadone 50 mg daily
NKDA

Social History

Heroin and cocaine abuse, last use 6 years ago. Currently enrolled in a methadone program.

Review of Systems

No weight changes, weakness, hot or cold intolerance, chest pain, shortness of breath, diarrhea, or constipation.

Physical Exam

HEENT: Conjunctivae: pale
Skin: Scalp: roughly 50% of total scalp hair preserved. Pull test revealed greater than 10% grasped hairs pulled from scalp from crown area. Areas of non- scarring alopecia most concentrated in the frontal and occipital regions. Eyebrows, eyelashes, axillae and groin: completely non-scarring alopecia.

Laboratory Data

The following initial labs were remarkable/abnormal:

Hemoglobin	8.9 g/dL	[11.7 – 14.9 g/dL]
Peripheral smear	Hypochromia, microcytosis	
MCV	69.4 fL	[81.8 – 96.9 fL]
RDW	19.6%	[12.3 – 15.6 %]
Iron	18 µg/dL	[45 – 182 µg/dL]
TIBC	456 µg/dL	[250 – 425 µg/dL]
Ferritin	3.0 ng/mL	[11.0 – 307.0 ng/mL]
Reticulocyte Count	0.8%	(0.3 – 2.7%)
Reticulocyte Index	0.4%	
Fe/TIBC	4%	
MCV/RBC	17.7	
Vitamin B12	122.0 pg/mL	[180 – 940 pg/mL]
Folate	6.87 ng/mL	[0 – 9 ng/mL]
TSH	0.090 µIU/L	[0.340 – 5.6000 µIU/L]
Free T3	3.53 pg/mL	[2.50 – 3.90 pg/mL]
Free T4	0.75 ng/dL	[0.58 – 1.64 ng/dL]
ANA	Negative	[Negative]
H. pylori IgG serum Ab	Positive	[Negative]

Gastrin	1427 pg/mL	[0 – 115 pg/mL]
Microsomal Antibody	1:1600	[<1:100]
Thyroid stimulating Ig	264 U	[0 – 139 U]
25-OH Vitamin D	13.8 ng/mL	(32.0 – 100.0 ng/mL)
AM Cortisol	5.76 µg/dL	[4.46 – 22.70 µg/dL]

The following labs were unremarkable/negative:
CMP, ANA screen, anticentromere antibody, hepatitis B screen, hepatitis C antibody, HIV 1/2 antibody, gliadin IgA antibody, tissue transglutaminase (endomysial) IgA antibody, thyroglobulin antibody, anti-mitochondrial antibody, and anti-smooth muscle antibody

Radiology (9/20/11)
CT scan abdomen/pelvis with contrast: no suspicious pancreatic, pulmonary, bowel masses or obstruction

Diagnosis
Type III polyglandular autoimmune syndrome (extensive alopecia areata; iron deficiency and pernicious anemia secondary to autoimmune chronic atrophic gastritis; and subclinical hyperthyroidism with thyroid-stimulating immunoglobulins)

Treatment and course
The patient initially presented with skin findings suggestive of extensive alopecia areata. However, given the patient's history of severe symptomatic iron deficiency, a thorough systemic evaluation was performed. The CBC, iron studies, Fe/TIBC ratio, and MCV/RBC ratio revealed ongoing iron deficiency anemia. The vitamin B12 level was also markedly reduced, which suggested possible autoimmune atrophic gastritis as the cause of the anemia. The presence of anti-parietal cell antibodies and a highly elevated serum gastrin (>12 times the upper normal limit) confirmed the diagnosis of an autoimmune chronic atrophic gastritis.

In addition, the initial thyroid panel was consistent with subclinical hyperthyroidism. While overt T3 thyrotoxicosis was ruled out, additional studies revealed thyroid stimulating immunoglobulins and thyroid antimicrosomal antibodies. In response to these clinical and laboratory findings, the patient was started on oral ferrous sulfate and intramuscular cyanocobalamin injections. Her hemoglobin rose to13.3 g/dL and her vitamin B12 level improved to >1500 pg/mL. Repeat thyroid function tests were normal. She was referred to endocrinology, who agreed with the diagnosis of type III polyglandular autoimmune syndrome once the AM serum cortisol levels were found to be normal (making the possibility of adrenocortical failure much less likely). CT of the abdomen/pelvis was negative for a neuroendocrine or gastric tumor as a source of the grossly elevated serum gastrin. The patient's alopecia proved refractory to topical corticosteroids, and she currently wears a hair prosthesis.

Discussion
Polyglandular autoimmune syndrome (PAS) includes a group of autoimmune disorders of the endocrine glands. First described in 1853 by Thomas Addison, who observed patients with adrenocortical failure in the setting of pernicious anemia, the entity was eventually expanded in 1980 to include 2 broad categories: PAS I (rare juvenile form) and PAS II (relatively more common adult type with adrenal failure), with the later addition of PAS III (which does not affect the adrenal cortex). PAS III can be divided into 3 subcategories. PAS IIIA is comprised of autoimmune thyroiditis with immune-mediated diabetes. PAS IIIB has autoimmune thyroiditis in the setting of pernicious anemia. PAS IIIC is defined as having autoimmune thyroiditis with alopecia and/or vitiligo and/or other organ-specific autoimmune disease (celiac disease, hypogonadism, myasthenia gravis, gastric carcinoid tumor, sarcoid, rheumatoid arthritis, etc).

Given that our patient had autoimmune thyroiditis associated with pernicious anemia and alopecia, while lacking any adrenal changes, she fit the criteria for a PAS IIIB/IIIC overlap syndrome.

Autoimmune, environmental, and genetic factors are all believed to play a role in pathogenesis of PAS. While the identification of circulating organ-specific autoantibodies provides the earliest evidence of polyglandular failure, cellular autoimmunity is also important. Histologic examination of affected glands (thyroid, parathyroid, gastric mucosa) has demonstrated a mononuclear infiltrate of macrophages, lymphocytes, NK, and plasma cells. Environmental factors, in particular viral infection, may serve to exaggerate the ongoing immune response and may precipitate or exacerbate glandular failure. PAS III also has a strong genetic component and tends to be clustered in individuals in the same family. Inheritance of the condition is postulated to be an autosomal dominant trait with incomplete penetrance and is associated with certain HLA class II genes. Specifically, alopecia areata is most strongly associated with the DQB1*03 and DRB1*11045 haplotypes, while the frequency of HLA-DRB1*0401 and DQB1*0301 is increased in patients with alopecia totalis and universalis.

In addition to lifelong hormone therapy for established endocrine organ failure, the care of patients with PAS includes frequent monitoring and familial screening for any signs of glandular dysfunction. Treatment of alopecia areata in these patients depends largely on age and severity and is similar to treatment in patients unaffected by polyglandular autoimmune syndrome. However, large-scale data regarding the likelihood of hair regrowth in this population is lacking, and it remains unclear if these patients are more refractory to treatment than those with isolated alopecia areata.

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Key location(s): Generalized **CASE 8**

Presented by Rachel Pritzker, MD; Hal Weitzbuch MD, MS; and Warren Piette, MD

History of Present Illness

52 year-old Hispanic female presented with an acute onset generalized rash. She had a one-year history of a mild, chronic eruption on the arms and legs diagnosed at an outside clinic as psoriasis, for which she took an unknown herbal supplement. Three days prior to admission, she developed a new, tender, bright red eruption on the arms and hands including palms. This quickly extended to her face, trunk, and legs. She reported associated fevers, chills, joint pain, and loss of appetite. Of note, fifteen days prior to onset of the new eruption, she started daily bupropion for depression. Bupropion was stopped one day prior to admission and she did not have any other new or changing medicines.

Past Medical History

Psoriasis
Depression

Medications/Allergies

Bupropion, calcium, unknown herbal supplement for psoriasis
NKDA

Review of Systems

Denied nausea, vomiting, cough, shortness of breath, headaches.

Physical Exam

Vitals T 100.3 ° F, P 100, BP 96/57, RR 20/min
Ill-appearing

Skin: Back: few well-demarcated hypopigmented and hyperpigmented patches
Face, trunk, arms: several small and large edematous bright red plaques with superimposed pinpoint and coalescing pustules
Palms: numerous red, non-scaling edematous papules
Scalp, back, arms including elbows, legs: several well demarcated, thin, red plaques with silvery scale
Nails: no changes

Laboratory Data

The following labs were remarkable/abnormal:

WBC	14.0 k/µL	[4.4 – 10.6 k/µL]
Neutrophil %	87.0 %	[45.3 – 74.5 %]
Lymphocytes %	6.2 %	[18.1 – 43.2 %]
CRP	10.06 mg/dL	[0.00 – 0.50 mg/dL]

The following labs were unremarkable/normal:
Na, K, Cl, HCO3, BUN, Cr, glucose, Mg, phosphorus, uric acid, total protein, total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, hemoglobin, hematocrit, platelet count, RPR

Histopathology

LEFT NECK, PUNCH BIOPSY:
Large subcorneal and spongiform neutrophilic pustules. Perivascular lymphocytic and neutrophilic infiltrate, with few eosinophils. Occasional dilated dermal blood vessels with mild red cell extravasation. Special stains for bacteria and fungi were negative.

LEFT UPPER THIGH, PUNCH BIOPSY:
Psoriasiform dermatitis with intracorneal and subcorneal foci of neutrophils, decreased granular layer, and dilated blood vessels in the papillary dermis.

Diagnosis
Generalized pustular psoriasis (von Zumbusch type) secondary to bupropion

Treatment and Course
The patient was admitted to the hospital for supportive care. During the first few days of admission, her skin lesions progressed, her fever rose to 102° F, and her WBC rose to 28.6 k/μL. Multiple negative blood cultures were obtained. On day three of admission, cyclosporine was started at 3mg/kg/day. Within one day, her skin lesions stabilized, and within two days exhibited notable improvement. Her fever remitted and her WBC slowly trended downward. On outpatient follow-up three weeks later, her skin eruption had resolved, with the normalization of her WBC and CRP. She was successfully tapered off the cyclosporine slowly over six weeks and was transitioned to topical corticosteroids for persistent, small psoriatic plaques. She remained clear of any new eruptions at the six-month follow-up visit.

Discussion
Bupropion is an atypical antidepressant used as an aid for smoking cessation. A member of the aminoketones class, it has a unique mechanism of action featuring the blockade of neuronal reuptake of norepinephrine and dopamine. Dermatologic side effects include pruritus, urticaria, serum sickness-like eruption, angioedema, generalized pustular and erythrodermic psoriasis, and subacute cutaneous lupus erythematosus.

Generalized pustular psoriasis (GPP) is a rare form of psoriasis characterized by a widespread eruption of sterile pustules on an erythematous base. There are several clinical subtypes of GPP, which include von Zumbusch type, annular type, acral type arising in the setting of acrodermatitis continua, exanthematic type, and the localized type. The von Zumbusch type is typically an acute, widespread eruption of pustules on a tender, erythematous base associated with systemic symptoms and leukocytosis. Often, this eruption is recalcitrant to standard treatments for psoriasis and is recurrent. In the first large review of GPP, Baker and Ryan reported two main subgroups of this disease. The first subgroup had a history of early onset of psoriasis with a typical chronic course and a generalized pustular flare provoked by an external agent. The second subgroup had a history of late onset, atypical psoriasis with a spontaneous generalized pustular flare. Since this report, a third subgroup of GPP arising without a history of psoriasis has been reported. Further, in another large case series by Zelickson et al., a majority of von Zumbusch type GPP patients had a prior history of psoriasis vulgaris and some had a history of localized pustular psoriasis.

Though the onset of GPP can be idiopathic, several factors have been implicated in precipitating an eruption, especially the withdrawal of systemic steroids. Other associated precipitants include infections, pregnancy, ultraviolet radiation, and several medications, including bupropion. A case report by Cox et al. describes three patients with a history of plaque psoriasis who presented with generalized pustular and erythrodermic psoriasis one to two weeks after starting bupropion. These patients discontinued the bupropion and were admitted to the inpatient ward for supportive treatment. All three of the patients were discharged between eight and fourteen days.

Acute generalized exanthematous pustulosis (AGEP) is also a widespread eruption characterized by numerous small, sterile pustules arising within large, erythematous plaques associated with fevers, leukocytosis, and a history of new medication use. The most common

precipitating medications are beta-lactam antibiotics, macrolides, calcium channel blockers, and antimalarials. There are no cases of AGEP from bupropion reported. Historically, many cases of AGEP have been diagnosed as GPP and vice versa.

The physical exam findings between the two can be indistinguishable. Signs favoring AGEP include short onset from new medication exposure (usually less than two days), shorter duration, spontaneous healing after cessation of medication, and lesions favoring the intertriginous skin and face.

Similar to the clinical presentation, the histopathology of the two eruptions is very similar, as they are both characterized by intraepidermal spongiotic pustules. Several sources comment that the histology of AGEP and an acute GPP eruption cannot be reliably differentiated. One recent study by Kardaun et al. investigated the comparative histological changes of these two conditions. They concluded that the presence of eosinophils, necrotic keratinocytes, a mixed interstitial and mid-dermal perivascular infiltrate, and absence of tortuous or dilated blood vessels favor a diagnosis of AGEP over acute GPP. Only the chronic lesions of GPP demonstrated an acanthotic or psoriasiform epidermal change. Moreover, in this study and others, patients diagnosed with AGEP had a higher prevalence of a personal history of psoriasis than the general population, making the diagnosis even more difficult to differentiate.

Overall, the diagnosis of GPP can be very difficult to determine versus AGEP. Our patient displayed worsening of her plaque psoriasis along with the acute onset of widespread, erythematous, edematous, tender plaques with pustules. These areas included the face and intertriginous areas, but were also widespread on the trunk and extremities. She was overall ill-appearing, had progression of her skin lesions with a leukocytosis up to 28.6 k/μL, and had a rising temperature over the first two days of admission. Furthermore, she had a history of taking bupropion, which has been associated with onset of GPP. She had been on the medication over 10 days prior to onset of the eruption, not three days or less, as seen in AGEP. Therefore, GPP precipitated by bupropion was the favored diagnosis, and we treated her with cyclosporine. She responded quickly and continues to do well on follow-up.

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Key location(s): Patient A – Left lower abdomen **Case 9**
Patient B – Right lower extremity

Presented by Michelle Chevalier, MD; David Reid, MD; and Jerry Feldman, MD

CASE A

History of Present Illness
53 year-old African-American female presented with a ten-year history of a malodorous, slightly pruritic eruption on her left lower abdomen that occasionally drained purulent material.

Past Medical History
Hyperlipidemia

Social History
No alcohol, tobacco, or illicit drug use

Medications/Allergies
Lovastatin
NKDA

Physical Exam
Skin: Left lower abdomen with linear, grouped, verrucous, slightly macerated papules

Histopathology
LEFT LOWER ABDOMEN, PUNCH BIOPSY:
Epidermis with focal area of acantholytic dyskeratosis and prominent suprabasilar clefting. Papillary dermis with dense lymphocytic infiltrate and rare eosinophils.

Diagnosis
Segmental Darier's disease

Treatment and Course
The patient was prescribed tretinoin 0.025% gel alternating with hydrocortisone 1% ointment daily. She was also treated with daily chlorhexidine gluconate 4% antiseptic skin cleanser. After five months, the patient noted a significant improvement in the appearance of her lesions, with resolution of the pruritus, malodor, and drainage. After one year, she continues to note excellent control of her disease.

CASE B

History of Present Illness
42 year-old African-American male presented with a four-month history of an extremely pruritic eruption on his right lower extremity, groin, and abdomen. He noted that the first lesion appeared on his right medial ankle with subsequent cephalad progression in a linear fashion up his posterior leg to his lower abdomen.

Past Medical History
Spinal stenosis
Right hip arthritis

Medication/Allergies
Hydroxyzine/NKDA

Social History
Positive for tobacco use. No alcohol or illicit drug use.

Physical Exam
Skin: Right medial malleolus, extending up posterior leg, groin, and upper abdomen with linear arrangement of hyperpigmented, flat-topped plaques; several with a surrounding ring of erythema

Laboratory data
The following were unremarkable/normal:
CBC, CMP, hepatitis panel

Histopathology
RIGHT UPPER LEG, PUNCH BIOPSY:
Epidermis with acanthosis, hyperkeratosis, and focal parakeratosis. Lichenoid interface dermatitis with vacuolar alteration of the basal layer. Papillary dermis with several melanophages.

Diagnosis
Linear lichen planus

Treatment and Course
The patient was initially treated with clobetasol 0.05% ointment twice daily for all affected areas except the groin, which was treated with hydrocortisone 1% ointment twice daily. After 2 weeks, he had much improvement with flattening and decreased pruritus of the linear eruption. However, he then noted a new eruption of pruritic lesions scattered on his trunk and upper thighs. This presentation was clinically consistent with generalized lichen planus and was successfully treated with triamcinolone 0.1% ointment twice daily. His lesions have all healed with significant post-inflammatory hyperpigmentation. He has recently noted flaring of the lesions on his right medial ankle.

Discussion
These cases of segmental Darier's disease and linear lichen planus are presented to highlight the phenomenon of mosaicism. Darier's disease is an autosomal dominant disorder caused by a mutation in the endoplasmic reticulum Ca^{2+} ATPase *ATP2A2*, encoding the protein product SERCA2. Lichen planus is an idiopathic inflammatory condition, likely with nonmendelian, polygenic inheritance. The occurrence of focal involvement of these conditions along Blaschko's lines (mosaic pattern type 1) is thought to occur as a result of mosaicism. Other less common patterns of cutaneous mosaicism have been described including blocklike (type 2), phylloid (type 3), large patches without midline separation (type 4), and lateralization (type 5).

Mosaicism occurs when there is a postzygotic event in embryonic development, leading to the mutation or non-disjunction of replicating chromosomes. This leads to the formation of two distinct cell populations, one with a pathogenic dominant mutation, and one with the corresponding wild-type allele. The closer this event occurs to fertilization, the greater the likelihood of significant phenotypic alteration and involvement of the germline. If the mutation occurs after the formation of gonadal cells, the germline will be free of mutation and the individual will not pass the mutation on to future generations. As Blaschko's lines are thought to represent the migrational route of embryonic ectodermal cells (i.e. keratinocytes, melanocytes), mosaic skin disorders often manifest in this pattern. The severity of cutaneous involvement depends on the timing of the mutational event in the embryo.

In cases of monogenic disorders such as Darier's disease, Rudolf Happle described two potential mosaic phenotypes. In type 1 mosaicism, a postzygotic heterozygous mutation occurs in a previously normal subset of cells. The affected individual will therefore manifest the disease in a segmental pattern only. In type 2 mosaicism, the patient already carries a germline mutation, with all cells of the body carrying a heterozygous mutation. There is then an additional postzygotic event, which results in a loss of the wild-type allele or "loss of heterozygosity." The phenotypic consequence of this occurrence is the diffuse manifestation of the disease in addition to a superimposed, often earlier onset and more severe segmental involvement. The localized, segmental findings in our patient with Darier's disease represent type 1 mosaicism.

In contrast to the monogenic nature of Darier's disease, lichen planus is a polygenic disorder. Happle has argued that the distinction between a "type 1" or "type 2" mosaic is not applicable in diseases of polygenic inheritance. It is impossible to differentiate between a heterozygous and a genetically normal embryo; therefore, the baseline status of the embryo is unknown. Given the frequent observation of coexisting segmental and generalized involvement in polygenic disorders, Happle has instead suggested the use of the less specific terms, "isolated" versus "superimposed" segmental manifestation. Our case of linear findings with subsequent generalization represents a case of superimposed linear lichen planus.

In inflammatory, polygenic, multifactorial, mosaic conditions such as linear lichen planus, it is has been proposed that there may be an environmental factor, such as a viral infection, which induces the expression of an unknown cutaneous antigen. This may serve as a trigger for a localized inflammatory T-cell response which manifests in a Blaschkoid pattern.

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Unknown D

What is the unifying diagnosis?

Please place your answer in the ballot box.