

Infectious Diseases Citywide Case

**Melissa Tiyouh, MD (1st year fellow)
Drexel University College of Medicine
Division of HIV Medicine and Infectious Disease**

CC: Fever, chills and weakness for 1 week

HPI: 40's yo Mexican male with no previous medical history presented with fever, chills and weakness x 1week

- Yellowish productive cough and dyspnea
- Fatigue, malaise, decreased appetite, night sweats x 1 month



- On a temporary work visa in the US for the past 2 months
- Lives in Mexico with his wife
- Works in pool remodeling in USA. Worked in Agriculture in Mexico

ROS

- Constitutional: + fever, +chills, + night sweats, + malaise, +decreased appetite, no significant weight loss
- HEENT: no sore throat, nasal congestion
- Respiratory: denies cough or hemoptysis, + dyspnea
- CVS: denies chest pain, palpitations
- GI: denies abdominal pain, diarrhea
- GU: denies dysuria or frequency
- Integumentary: no rash
- MSK: denies joint pain
- Neuro: denies confusion or loss of sensation

PMH: None

Allergies: NKDA

Meds: none

PSH: none

FH: Mother died of Cancer (unknown type)

Social Hx: Denied tobacco, alcohol or illicit drugs

Physical exam

Vitals: 102.8 F, HR=108, BP= 95/60, RR=31, 97% RA

- Gen: lethargic
- HEENT: dry mucous membranes. icteric sclera
- Neck: No cervical lymphadenopathy
- Lungs: mild rales in RUL, no wheezing
- CVS: tachycardic, no murmurs, rubs, gallops
- Abd: Soft, non- tender, non- distended. Positive BS
- Skin: diffuse ecchymosis in bilateral upper and lower extremity.
- Neuro: no focal deficits

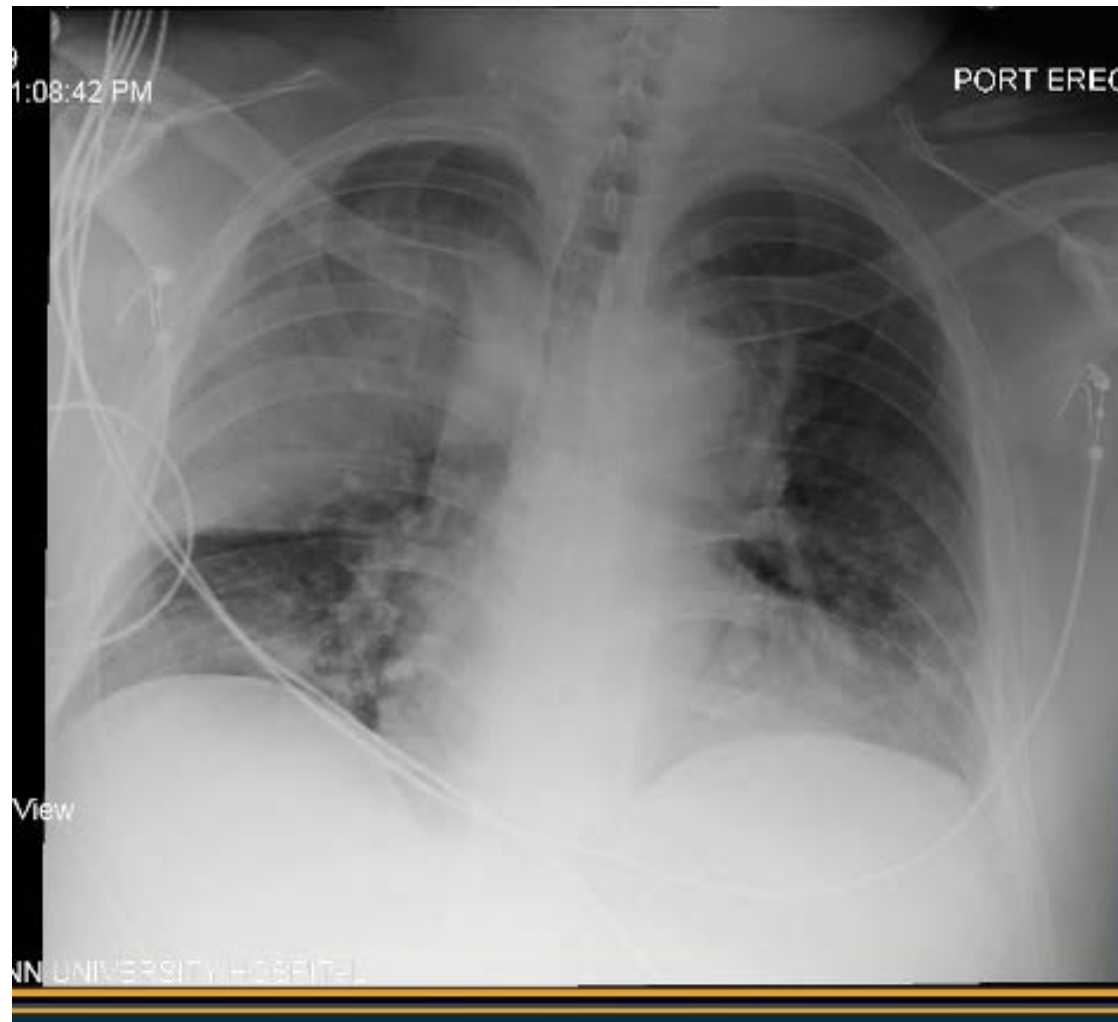
Labs

- WBC 0.1 ANC 0
- Hb 5.8/Hct 19
- Platelets 7
- Albumin 2.2
- Alk Phos 159, ALT 111, AST 142, Tbili 5.64
- Bun 26
- Creatinine 1.12
- Rapid HIV neg
- Viral hepatitis panel neg
- Blood culture negative

Hospital Course

- Started on empiric vancomycin and pip-tazo
- CXR was consistent with pneumonia
- Completed 14 days of vanc/pip-tazo with resolution of pneumonia

CXR





Hospital Course

- Pt was diagnosed with B cell Acute lymphoblastic leukemia (ALL)
- Induction therapy with Cyclophosphamide, Daunorubicin, Vincristine and Prednisone
- Received intrathecal methotrexate via ommaya reservoir

Hospital Course

- Started on levofloxacin, TMP/SMX, valacyclovir and voriconazole chemoprophylaxis
- Voriconazole was held 3 weeks later secondary to chemo-induced liver injury



Hospital Course

- Complicated and prolonged hospital course with multiple ICU admissions due to:
 - Chemotherapy
 - Neutropenic fevers
 - VRE BSI from line infection
 - C diff colitis
 - UTI
 - PE
 - Social placement (undocumented)

Hospital Course

- 4 months into his course, he completed induction and one cycle of consolidation chemotherapy with hematologic remission
- Developed L eye redness and decreased vision
- Lethargy and headaches

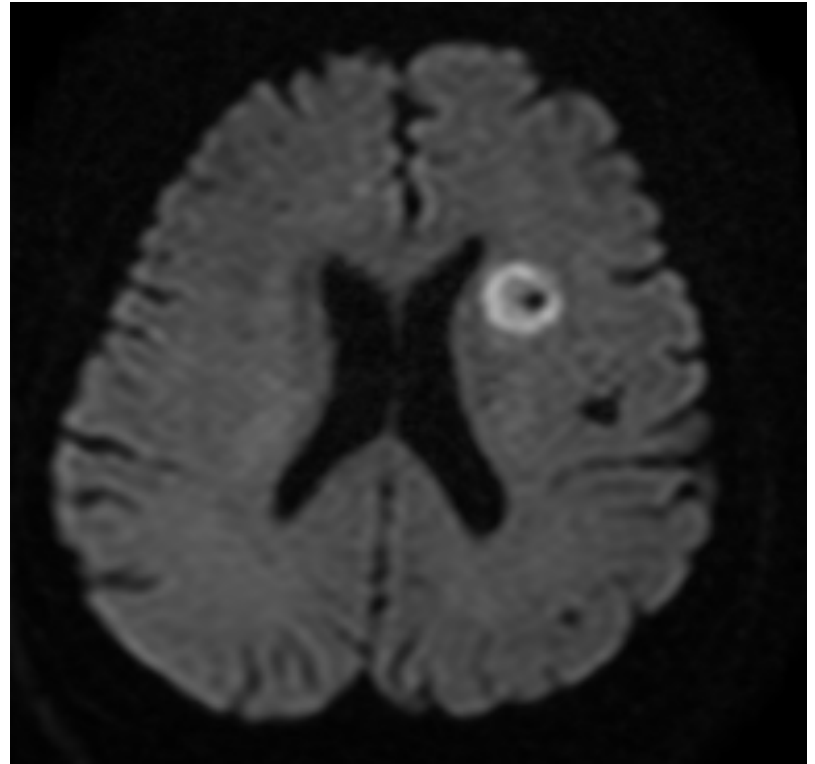
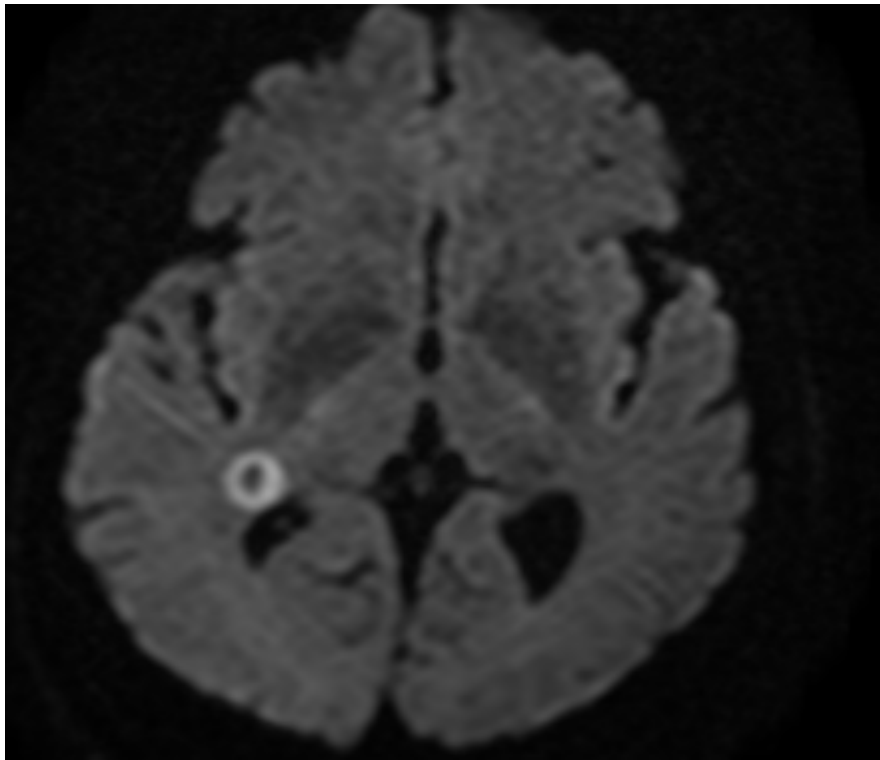


Hospital Course

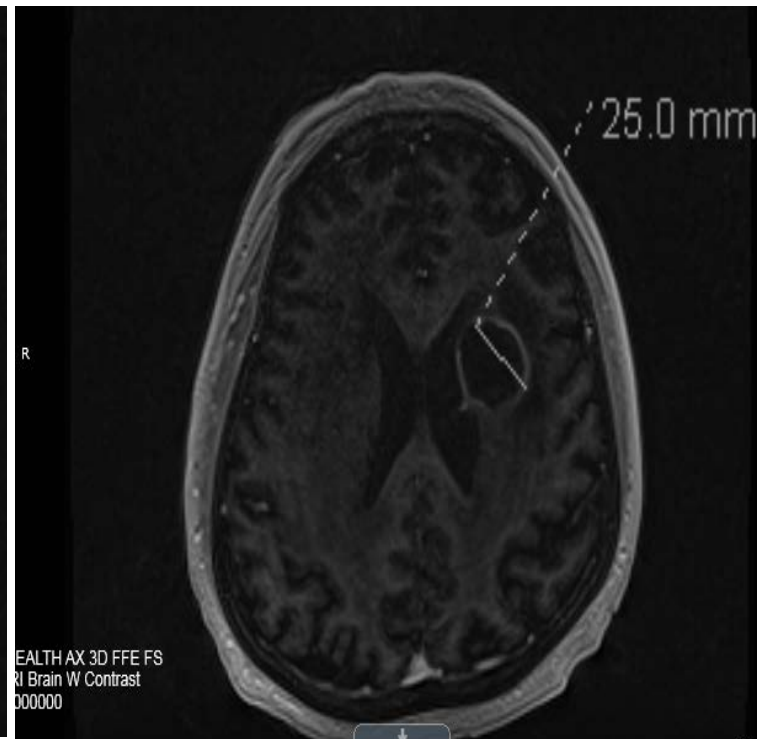
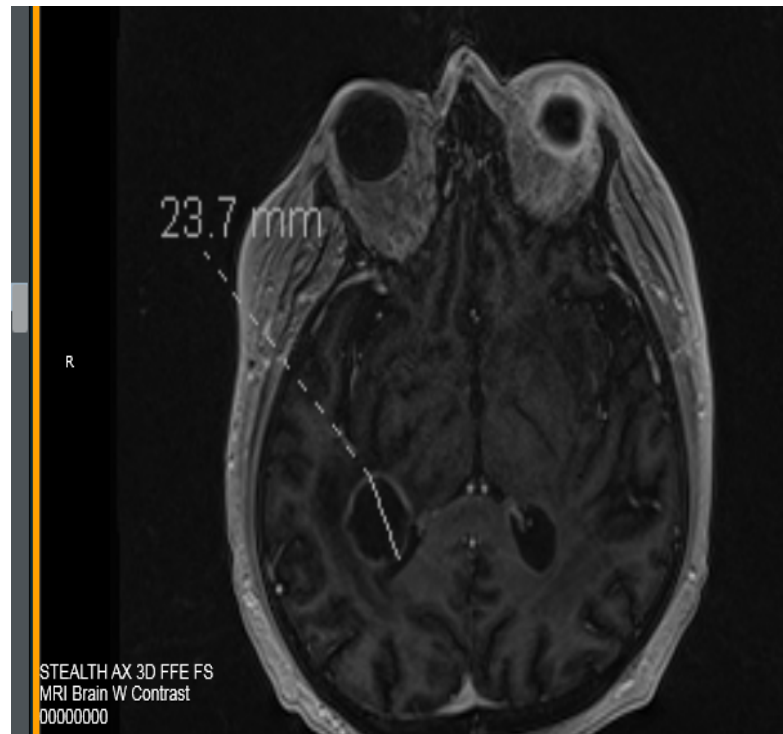
- Ophtho performed diagnostic vitrectomy, which revealed **solid L. choroidal lesion**



Brain MRI



Brain MRI



CSF analysis via ommaya reservoir

- WBC 2
- Glucose 77
- Protein 15



Summary

- 40's yo Mexican male admitted with Pneumonia and severe pancytopenia. Diagnosed with B-cell ALL s/p Larson chemo regimen and IT Methotrexate with hematologic remission. 4months later, developed Left eye vision loss. PPV revealed L choroidal lesion and brain MRI with rapidly growing ring enhancing lesions

Differential diagnosis ?

Differential diagnosis

- Infectious etiologies
 - Toxoplasmosis
 - TB/Tuberculoma
 - *Mucor*
 - *Fusarium*
 - *Aspergillus*
 - *Cryptococcus*
 - *Candida*
 - *Nocardia*
 - *Pseudallescheria/Scedosporium*
- Non-Infectious causes
 - Leukemia or lymphoma
 - Demyelinating syndrome

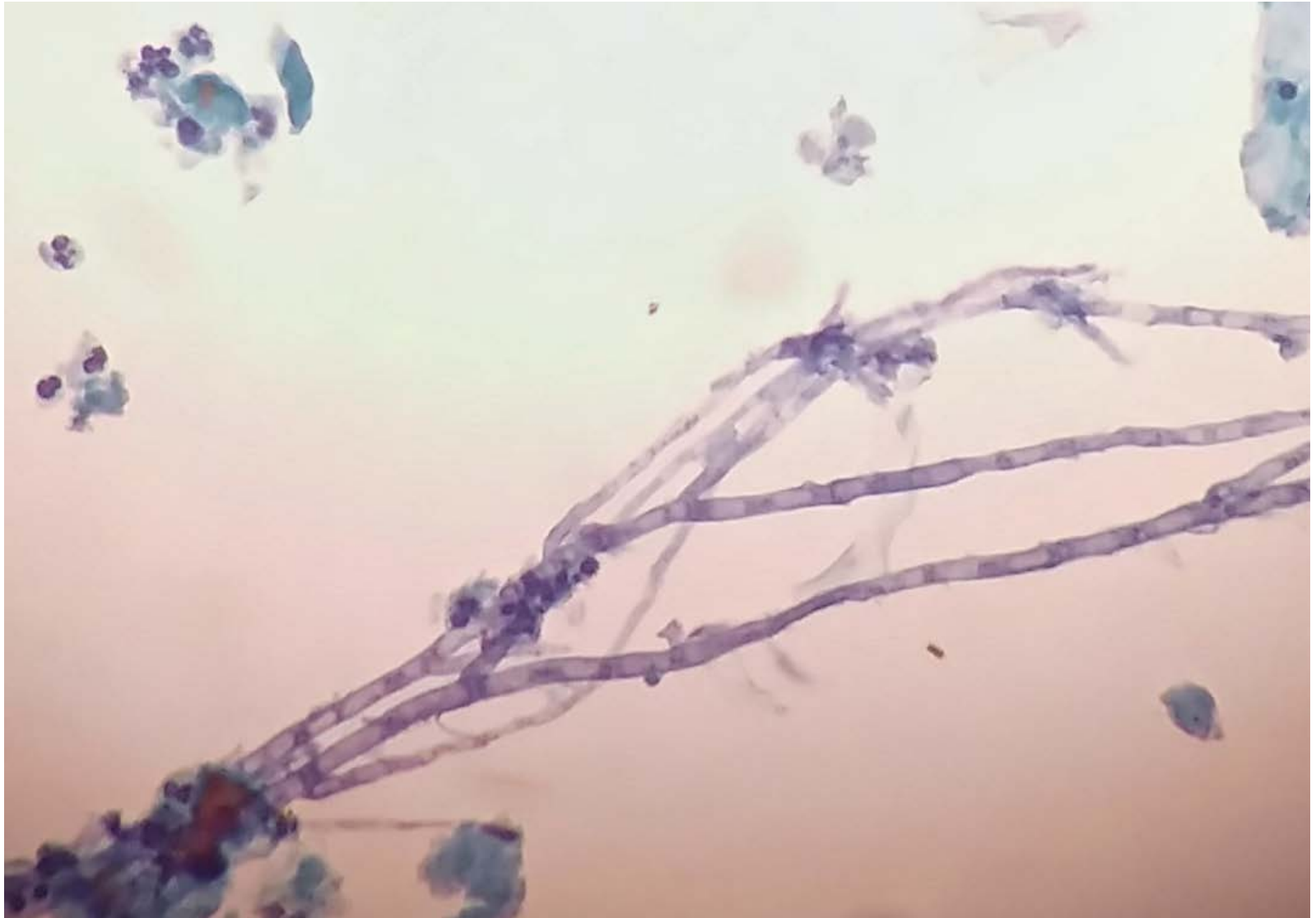


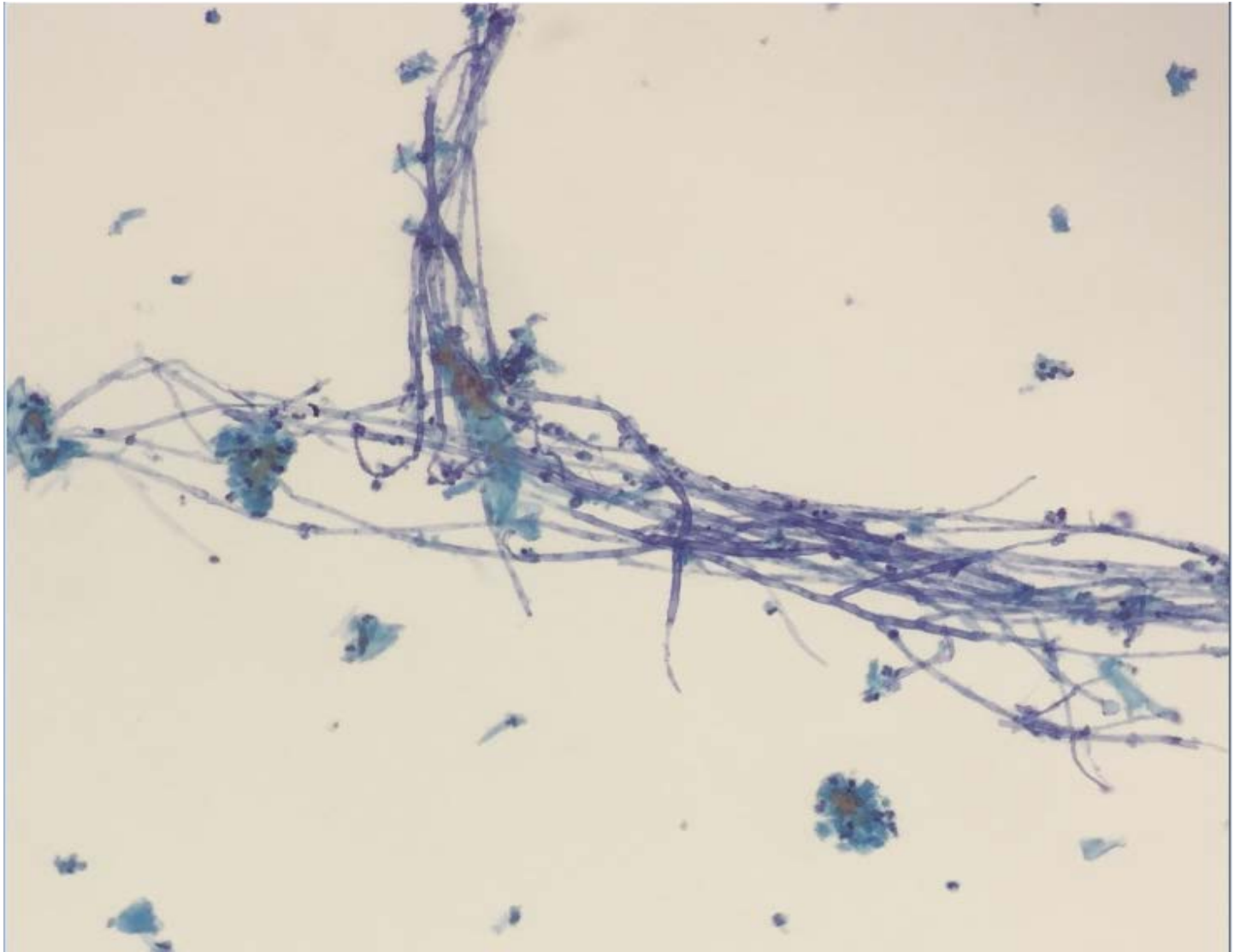
Hospital Course

- Received intravitreal vanc, ceftazidime and amphotericin B with no improvement in vision
- ID recommended empiric pyrimethamine + sulfadiazine and liposomal amphotericin B
- Underwent left frontal and right temporal stereotactic biopsy and drainage of abscesses

Results

- CSF culture - neg
- Serum and CSF Aspergillus Ag neg
- Serum and CSF Cryptococcal Ag – neg
- Toxoplasma PCR -neg
- Blood cx – neg
- B-d-glucan 36- >452



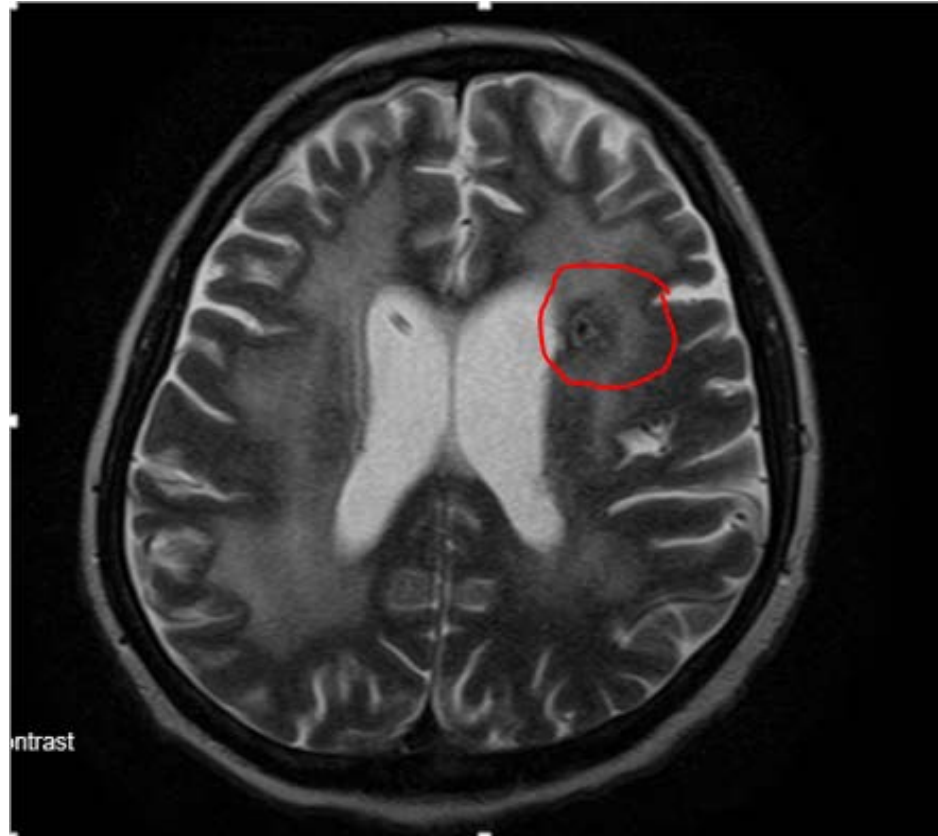




Hospital Course

- Started on voriconazole and continued on Amphotericin B
- CT chest showed multiple nodular infiltrates
- Vision and clinical symptoms improved
- He was medevac-ed to Mexico to complete 12 week course of voriconazole and LAM

2 months after therapy



Invasive Aspergillosis

Introduction

- Identified by Italian botanist/Priest Micheli in 1729
- Named after Aspergillum (holy water sprinkler)



- *Aspergillus* can be found in water, food, air, and soil
- Infection occurs primarily in immunocompromised hosts

Introduction

- *Aspergillus fumigatus* is the most common infecting species
 - other species include: *A. flavus*, *A. terreus*, and *A. niger*
- Invasive aspergillosis most commonly involves the lungs
- Can disseminate beyond the respiratory tract to multiple organs, including the skin, brain, eyes, liver, and kidneys
- Disseminated infection is associated with a very poor prognosis



Risk factors

- Prolonged neutropenia (<500 cells/mm³ for >10 days)
- Transplantation (highest risk is with lung and HSCT)
- Prolonged (>3 weeks) and high-dose steroid therapy
- Hematological malignancy
- Cytotoxic therapy
- Advanced AIDS
- Critically ill patients

Am J Respir Crit Care Med 2006;173:707-17

CNS Aspergillosis

- From disseminated infection
- Local extension from the paranasal sinuses
- Mycotic aneurysms develop in some cases and can rupture
 - hemorrhagic CVA
 - subarachnoid hemorrhage
 - empyema



Ocular Aspergillosis

- Can present as:
 - Dacryocystitis
 - Periorbital cellulitis
 - Endophthalmitis
 - Vitritis
- Also from contiguous extension from invasive sinusitis or hematogenous spread
- The highly vascular choroid is seeded first



Diagnosis

- *Aspergillus* grows well on standard media
- Definitive diagnosis requires tissue biopsy
- CSF analysis is not typically useful



Non Invasive tests

- Two FDA approved laboratory markers
 - Serum Galactomannan assay
 - Serum B-D-glucan assay
- Serum and BAL Aspergillus PCR

Aspergillus Lateral Flow Device



Aspergillus LFD

- Rapid response in 10-15minutes
- Uses JF5 mAb that binds to an extracellular glycoprotein secreted during active growth of Aspergillus
- Tested for Serum and BAL specimens





Treatment

IDSA 2016 guidelines....

- Recommend voriconazole as primary therapy for invasive aspergillosis
- Amphotericin B is reserved for those intolerant or refractory to voriconazole



Isavuconazole (Cresemba)

- **SECURE** trial
 - Phase 3, double-blind, global multicenter, comparative study
 - Assessed efficacy and safety of isavuconazole versus voriconazole in patients with invasive mold disease
 - 527 adult patients between March 2007 and March 2013
 - Concluded isavuconazole was non-inferior to voriconazole for the primary treatment of invasive mold disease
 - Better tolerated
 - Has fewer adverse effects and drug-drug interactions



Posaconazole “Noxafil”

- Approved for prophylaxis of invasive fungal infections
 - Superior survival in Patients with AML and Myelodysplastic diseases
- 2nd-line treatment of invasive aspergillosis
- Retrospective studies demonstrated benefit for salvage therapy

Walsh TJ et al.: Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: Clin Infect Dis 2007,44(1):2–12. 10.1086/508774



Combination Therapy

- Used for severe infection, especially CNS involvement
- Appropriate option for refractory and/or resistant cases
- Evidence of synergy and improved outcome with Azole—echinocandin
- In vitro studies also support combination of a polyene with an echinocandin or a polyene with an azole



Duration

IDSA Guidelines...

- Minimum of 6–12 weeks therapy
 - Dependent on the degree and duration of immunosuppression
 - Site of disease
 - Evidence of disease improvement
- Patients who recover from an episode of invasive aspergillosis are at risk for recurrence during subsequent immunosuppression



Azole Resistance

- Azole resistance in clinical *Aspergillus* isolates has been linked to mutations in the ***CYP51A*** gene.
- Treatment is challenging and Patients are usually treated with combination therapy

Take home points

- Voriconazole remains the recommended therapy for invasive aspergillosis.
- New antifungal agents like isavuconazole and new formulations of posaconazole offer the potential for improved outcome in patients with invasive aspergillosis.
- The role of combination therapy remains controversial but can be considered in high risk patients like those with hematological malignancy and severe disease.
- Prophylaxis may improve outcome in high risk patients.

References

- Invasive Aspergillosis, Jose Cadena MD, George R. Thompson MD and Thomas F. Patterson MD. Infectious Disease Clinics of North America, 2016-03-01, Volume 30, Issue 1, Pages 125-142, Copyright © 2016
- Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, Kern WV, Marr KA, Ribaud P, Lortholary O, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002;347:408-415.
- Marr KA, Boeckh M, Carter RA, Kim HW, Corey L. Combination antifungal therapy for invasive aspergillosis. Clin Infect Dis 2004;39: 797-802.
- Aspergillus-Specific Lateral-Flow Device and Real-Time PCR Testing of Bronchoalveolar Lavage Fluid: a Combination Biomarker Approach for Clinical Diagnosis of Invasive Pulmonary Aspergillosis. Gemma L. Johnsona, Shah-Jalal Sarkerb, Francesco Nanninia
- Diagnostic accuracy of a novel lateral-flow device in invasive aspergillosis: a meta-analysis, Zhijie Pan, Mengjiao Fu, Jiaojiao Zhang, Hua Zhou, Yiqi Fu and Jianying Zhou
- IDSA Guidelines
- Azole Resistance in Aspergillus fumigatus: Can We Retain the Clinical Use of Mold-Active Antifungal Azoles? Paul E. Verweij,¹ Anuradha Chowdhary,² Willem J. G. Melchers,¹ and Jacques F. Meis^{1,3}
- Walsh TJ, Raad I, Patterson TF, et al.: Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. Clin Infect Dis 2007,44(1):2–12. 10.1086/508774

Diarrhea in an Immunocompromised Patient

Nabil Zeineddine

1st year ID fellow

Drexel College of Medicine

HPI

- 70's y.o. M transferred to HUH from nursing home.
- CC: Watery, non-bloody diarrhea, >8 BMs/day for 5 days, in January
- Usual state of health prior to onset of diarrhea, mobile, performs ADLs
- Lives at senior apartment complex, independent living

ROS

- No abdominal pain
- No fever
- No jaundice
- lethargy +

Physical Exam

- BP 50s/30s on arrival
- Temp 91.2, HR 115, RR 18, Sat 100% 3LNC
- Somnolent, AAO*1 , diminished pulses in all extremities
- Abd: soft, NT/ND, +BS
- Cardiac: sinus tachycardia
- Resp: CTA b/l, although not taking full breaths

Labs

- ABG: 7.07/15/188/4.2
- Creatinine 4.9, BUN 145
- K 7.5

Initial Treatment

- IVF, albumin
- Started on norepinephrine via CVC
- Given vancomycin, cefepime, levofloxacin empiric abx for severe septic shock
- Checked C diff stool assay
- Blood x2 and urine culture sent
- Transfer to HUH after <24 hrs

Additional History

- PMHx:
 - OHTx 2000 for ischemic cardiomyopathy, on Tac/MMF
 - A-flutter s/p ablation
 - LCW PPM 2009
 - HTN, HLD, BPH
- SHx:
 - nonsmoker, social EtOH, no drugs
- PSHx:
 - OHTx

Medications

- Tacrolimus 1mg PO BID
- Mycophenolate 500mg PO BID
- Simvastatin 40mg PO daily
- Rivaroxaban 15mg PO daily
- Finasteride 5mg PO daily
- Carvedilol 6.25mg PO BID
- Alendronate 70mg PO weekly
- Dofetilide 125mcg PO daily
- Lasix 40 mg PO PRN
- Lisinopril 10mg PO daily
- Calcium/Vitamin D

Labs at HUH

- WBC 7000, 80% PMN, 8% L, 10% M
- AST 8, ALT 4
- Alk Phos 34, T bili 0.8 mg/dl
- Trop 0.7
- BUN/Cr: 113/3.17
- *C. diff* toxin negative

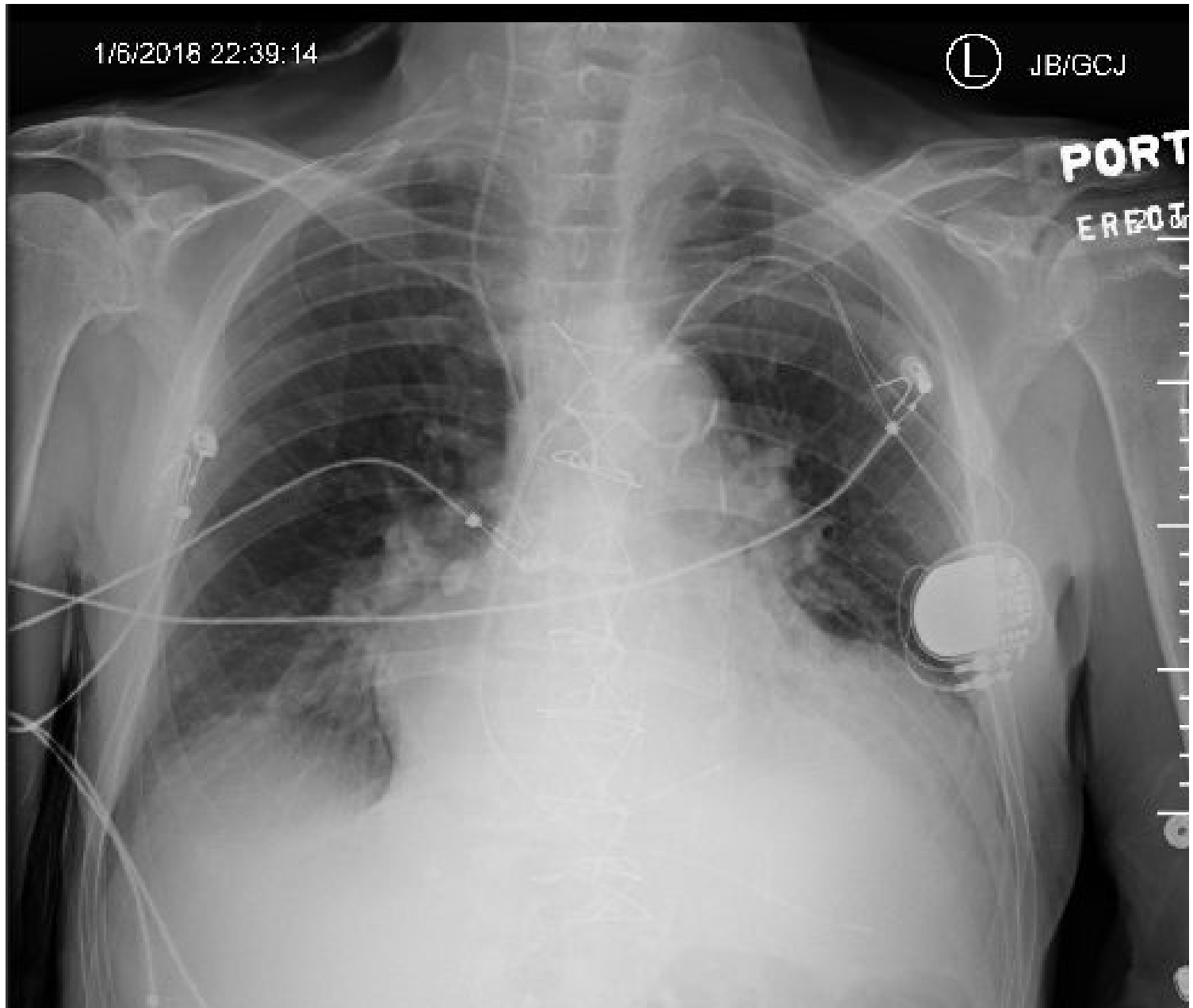
1/6/2018 22:39:14



JB/GCJ

PORT

ERECT



Additional Information

- Lives at senior independent living apartment complex
- Reported several sick contacts at center
- Had holiday group meal ~6 days prior to symptom onset
- No recent antibiotic exposure known nor hospitalization in six months
- No history of uncooked food or eating from street vendors
- Rejection episodes 2013, 2015, 03/2017, treated with Solumedrol

So Far...

- 79 y.o, M, OHTx on immunosuppression, with 5 days diarrhea, in shock and multi-organ failure.
- **Additional information?**
- **Differential diagnosis?**



Diarrhea in transplant recipients	
Infectious	Noninfectious
Bacterial <i>C. diff</i> <i>Campylobacter</i> <i>Salmonella</i> <i>Aeromonas, E coli</i> MAI	IS medications MMF Tacrolimus Cyclosporine Sirolimus
Viruses CMV <i>Norovirus</i> <i>Rotavirus</i> <i>Adenovirus</i>	Other GVHD PTLD
Parasitic <i>Giardia</i> <i>Cryptosporidium</i> <i>Isospora, Cyclospora, Microsporidium</i> <i>Entameoba</i>	

ID Consult

- Sent stool for culture, Shiga toxin, O/P, Acid Fast staining, *Cryptosporidium* Ag, *Norovirus* Ag.
- Serum CMV PCR Quantitative
- MMF held

Results

- CMV PCR Quantitative = negative
- Stool studies for *Salmonella*, *Shigella*, O/P, *Campylobacter* = negative
- Blood cultures from HUH and at Inspira Hospital = negative

Stool *Cryptosporidium* Ag = POSITIVE

Hospital Course

- Diagnosed with hypovolemic shock secondary to Cryptosporidiosis
- Started on nitazoxanide 500mg PO BID
- MMF stopped
- Remainder of antibiotics stopped
- Patient's condition improved, pressor weaned, renal function improved, eventual discharge
- Seen in heart failure office one month later & symptoms all resolved

Cryptosporidiosis reported to NJ DOH

Week 1 of 2018	0
Week 2 of 2018	1
Week 3 of 2018	0
Week 4 of 2018	0

Outbreak of Cryptosporidiosis at a Day Camp -- Florida, July-August 1995

On July 27, 1995, the Alachua County Public Health Unit (ACPHU) in central Florida was notified of an outbreak of gastroenteritis among children and counselors at a day camp on the grounds of a public elementary school. This report summarizes the outbreak investigation, which implicated *Cryptosporidium parvum* as the causative agent and underscores the role of contaminated water as a vehicle for transmission of this organism.



Foodborne Outbreak of Cryptosporidiosis -- Spokane, Washington, 1997

On December 29, 1997, the Spokane Regional Health District received reports of acute gastroenteritis among members of a group attending a dinner banquet catered by a Spokane restaurant on December 18. The illness was characterized by a prolonged (3-9 days) incubation period and diarrhea, which led public health officials to suspect a parasitic cause of the illness. Eight of 10 stool specimens obtained from ill banquet attendees were positive for *Cryptosporidium* using both modified acid-fast and auramine-rhodamine staining of concentrated specimens. This report summarizes the epidemiologic investigation of the outbreak, which suggests that foodborne transmission occurred through a contaminated ingredient in multiple menu items.



Outbreaks

- Massive outbreak in 1993 in Milwaukee transmitted through public water system contaminated by oocytes that passed through the filter of water treatment plant
- 403,000 cases of watery diarrhea

Milwaukee *Cryptosporidium* outbreak

Clinical characteristics of lab confirmed Cryptosporidiosis	
Diarrhea	100%
Watery diarrhea	93%
Abdominal pain	84%
Fever	57%
Vomiting	48%
Mean duration of diarrhea	12 days
Mean max no. of stools/day	19

McKenzie WR et al. A massive outbreak in Milwaukee of cryptosporidium infection transmitted through the public water supply. N Engl J Med. 1994 Jul 21;331(3):161-7

Presentation

- Incubation period 2-10 days, average ~7 days
- Food and waterborne or animal-human transmission (*C. parvum*)
- Immunocompromised patients may have severe and/or life threatening presentation
- 10-15% AIDS patients with biliary involvement



Etiology	Community-Onset Diarrhea (n = 422)		Hospital-Onset Diarrhea (n = 112)		P Value
	No.	%	No.	%	
Single diagnosis (n = 523)					.03
NOS	257	60.9	85	75.9	
<i>Clostridium difficile</i> infection	55	13.0	13	11.6	
Norovirus	34	8.1	3	2.7	
CMV disease/colitis	26	6.2	3	2.7	
Other ^a	42	10.0	6	5.4	

Clinical Infectious Diseases, Volume 60, Issue 5, 1 March 2015, Pages 729–737, <https://doi.org/10.1093/cid/ciu880>

Which one eradicates *Cryptosporidium* spp?



Which one eradicates *Cryptosporidium spp*?



Treatment Options

- Often self-limited illness in immunocompetent patients
- Symptoms last 1-2 weeks, can shed oocysts up to 4 weeks, even if symptoms resolve
- Nitazoxanide or paramomycin for immunocompetent x3 days
- AIDS = ART
- Transplant = decrease immunosuppression

Transplant Guidelines

- Cyclosporine metabolites demonstrate in-vitro activity
 - *Cryptosporidium*
 - Malaria
 - *Toxoplasma*
 - Schistosomiasis

Cryptosporidium

Nitazoxanide 500 mg po bid x 14 days (same as for HIV+)

(pediatric: 12–47 months of age, 100 mg PO bid
4–11 years of age, 200 mg PO bid \geq 12 years
of age – see adult dosing)

Reduce immunosuppression if possible

Paromomycin or azithromycin; consider
combination therapy

American Journal of Transplantation 2013; 13: 280–303

Prevention

- Wash hands with soap and water
- Alcohol-based sanitizers and chlorine ineffective
- Boiling water
- <1 micron water filter

THANK YOU!

Mystery Eschar

City Wide conference 4/24/18
Marinela Ingilizova
ID fellow Drexel University

HPI

- 80's y/o Asian American with PMH of DM, HTN, prostate cancer presents with acute change in mental status for few hours duration
- Patient was found by his wife to be confused, disoriented, and auditory hallucinations.
- He was afebrile did not have any other complaints.

HPI

- Patient had been discharged the night before after 3 days hospitalization where he was found to be febrile (Tmax 102), with AKI and hyponatremia
- CXR with bilateral opacities, patient was started on empiric vancomycin and cefepime
- Blood cultures and urine cultures negative
- CXR opacities as well as hyponatremia improved after diuresis

Additional History

- **Allergies:** none
- **PMH:** DM HTN Prostate cancer radiation 7 years ago leupron 2 months ago
- **PSH:** none
- **FH:** noncontributory
- **SH:** lives at home with wife, not sexually active, never a smoker, denies IVDU or alcohol abuse, immigrated from South Korea 1976 and lived in the USA ever since

Additional History

- **Vaccinations:** UTD
- **Pets:** Has a dog at home
- **Occupation:** Retired dentist
- **Travel:** Seoul, Korea and “rural area north of the capital” 10/17 to 11/02. Spent one day in Seattle WA on the way back home. Had bottled water, did not swim or hike, was in air conditioned environment while in Seoul, did not eat street meat or uncooked food

Physical Exam

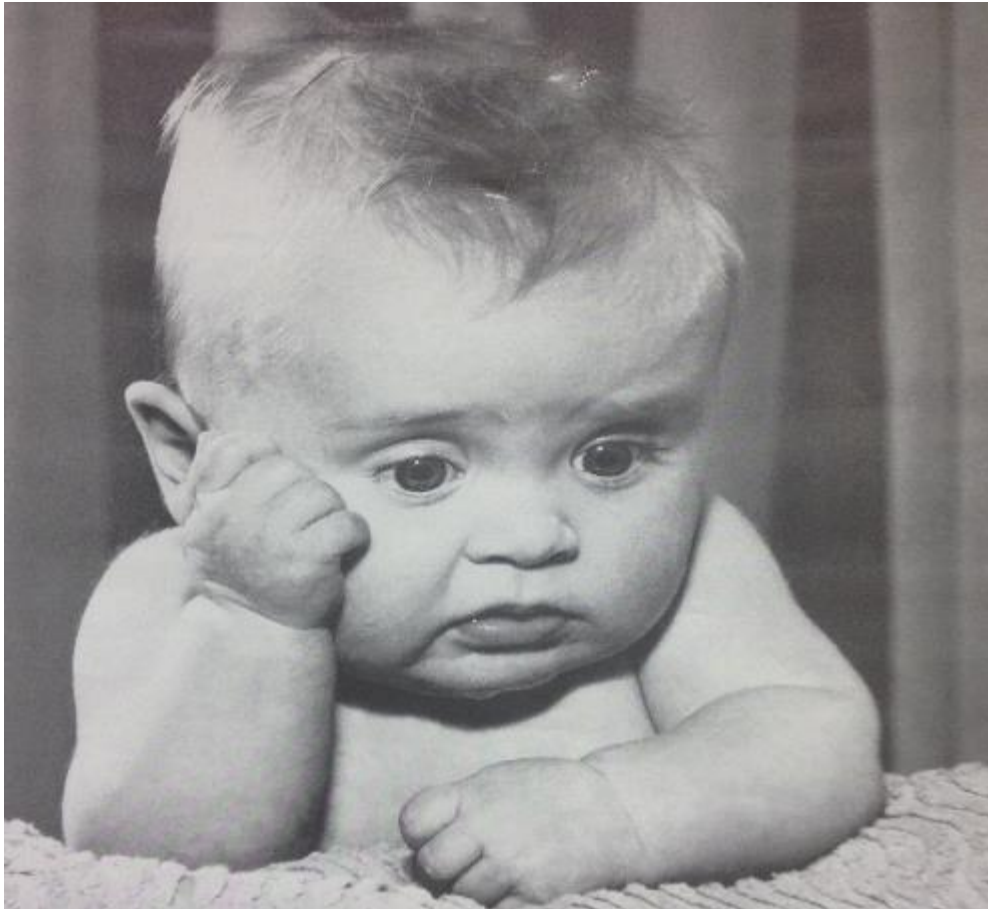
- T 98.0, BP 110/80 HR 72 RR 18 saturating 95 % on RA
- AO to self and place, no speech deficits
- Had memory loss for immediate preceding events
- CN II-XII intact, motor strength 5/5 in all 4 extremities
- PERLA anicteric sclera
- Neck supple
- No lymphadenopathy axillary inguinal or cervical
- CTAB
- S1 S 2 no rubs or gallops PP+
- Joints - unremarkable
- Extremities no peripheral edema
- Skin - rash



Studies

- Images including CXR, MRI of brain, ultrasound of liver- Normal Echocardiogram - unremarkable
- Labs:
 - WBC 9.0 HH 13/30 Plt 125 (3 months ago 225)
 - AST/ALT 115/92 T billi 1.3 Alk phos 110 Alb 3.2
 - BUN/Cr 17/1.13 Na 135 BNP 135
 - UA 180 RBC, negative leuk esterase WBC 23
- Micro:
 - BC negative x 2
 - Flu swab negative
 - HIV - Hep A, B and C serology negative

Differential diagnosis ????????



Differential

- Rickettsial disease: *R. acari* (Rickettsial Pox), *R. parkari*, *Orientia tsutsugamushi*, *R. africae*, *R. conorii*, *R. honei*, *R. japonica*, *R. sibirica*
- Cutaneous Anthrax
- Ecthyma
- Spider bite
- Ehrlichiosis, Anaplasmosis
- Malaria

Studies

- Biopsy of the eschar
- Blood smear
- Blood work for serology and PCR for *Rickettsia*

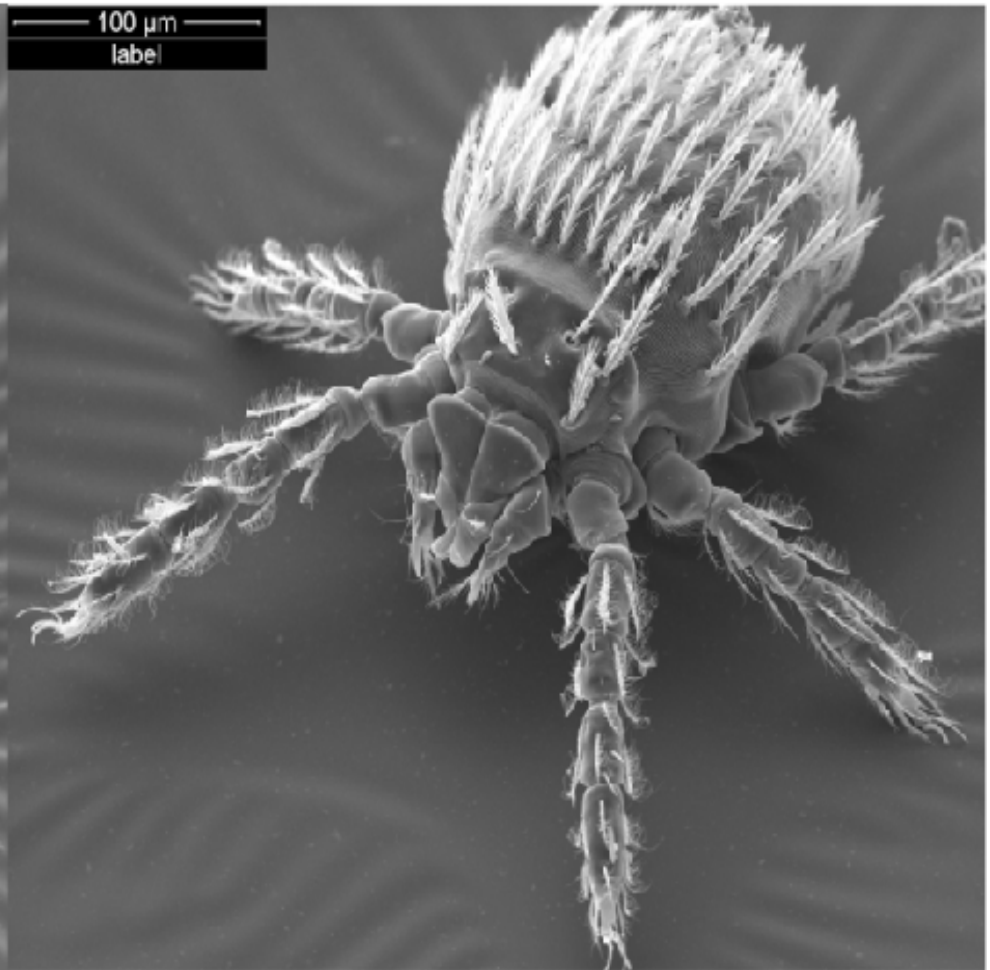
Results

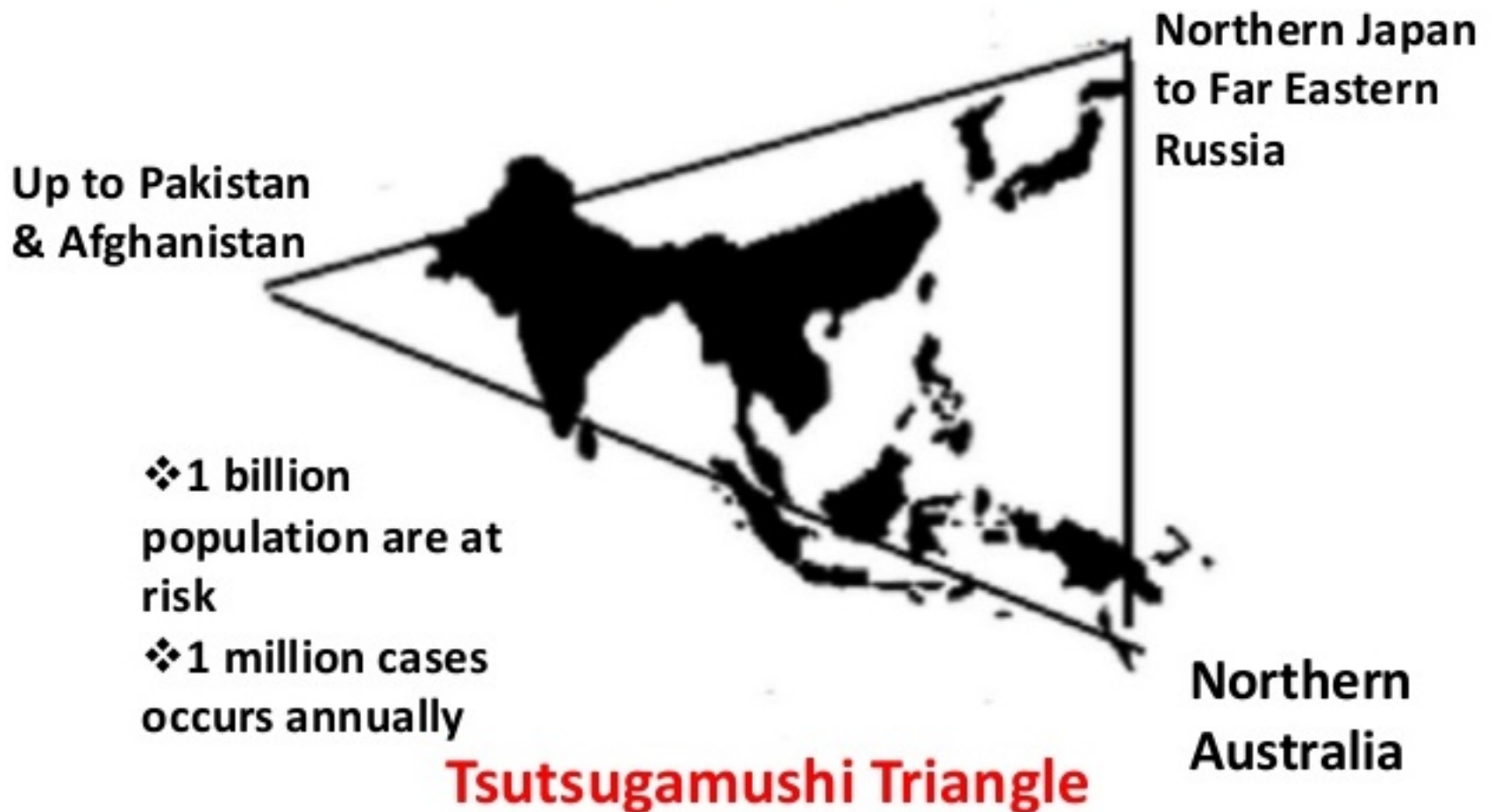
- Pathology from the eschar – “superficial leukoclastic vasculitis with suppurative necrosis”
- Blood smear unremarkable
- PCR blood for *Anaplasma* and *Ehrlichia*: negative
- PCR serum for *Orentia Tsutsugamushi*: negative
- Serum IgG for *Orentia Tsutsugamushi* - 2048
- PCR biopsy for *Orentia Tsutsugamushi* - positive

Scrub Typhus

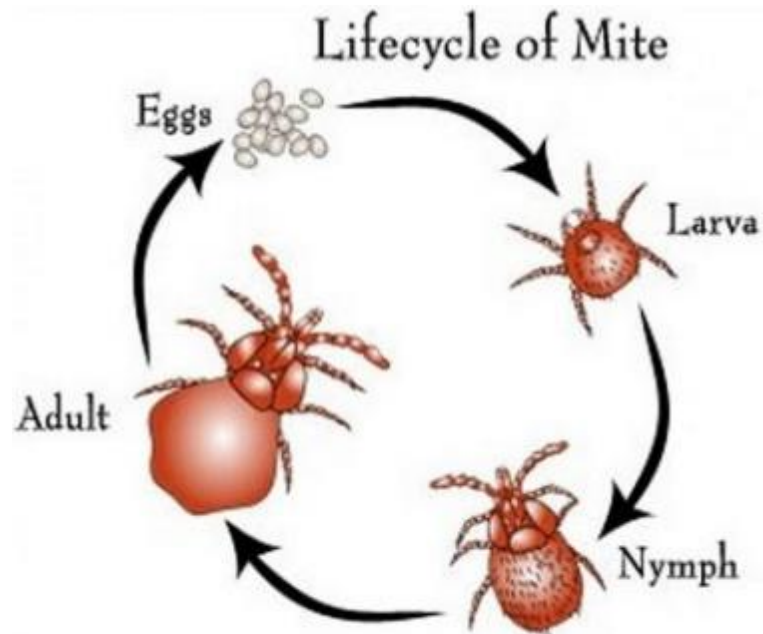
- *Orientia Tsutsugamushi* is the causative organism of scrub typhus
- In Japanese “Tsutsuga” - illness and “Mushi ” - insect
- Rickettsiaceae family
- Arthropod - bourn obligatory intracellular bacillus
- Unique trilaminar membrane
- July - November
- Febrile illness 7-10 days after exposure - can be with insidious or abrupt
- Delirium, pneumonitis, AKI, nausea, vomiting, diarrhea, meningitis

Vector is mites (Leptotombidium)





Larva (chiggers) → nymph → adult → egg



<http://www.medindia.net/patients/patientinfo/scrub-typhus.htm>

- Tropical climate with high temperature and humidity
- Wooded areas, rice fields
- Some cases of scrub typhus transmitted with blood transfusion have been described

Diagnosis

- Tissue
- Eschar - skin biopsy - placed on sterile gauze can be moist with sterile saline in a sterile collection cup (tissue should not be immersed into saline)
- Molecular detection is most sensitive during the first week of acute illness and within 24h of appropriate therapy
- Swab of the eschar is also acceptable or the scab can be submitted for testing
- Specimens should be placed on cold packs or freeze at 70 C
- The specimens should be sent to CDC via the State Health Department lab

Treatment

- Doxycycline is the drug of choice 100 mg bid IV or PO
- Duration of therapy is uncertain
- Generally 5 - 7 days
- Shorter durations are related to relapses
- Azithromycin 500 mg single dose can be an alternative to resistant to doxycycline strains

Treatment

- Several studies have demonstrated efficacy of long - acting tetracycline
 - Doxycycline - started 3 days before exposure and given weekly continued 6 weeks post exposure
- Active or passive immunity is not possible
- Patients who had the disease may get re-infected
- Enormous antigenic variation in multiple strains
- Treat clothing and gear with Permethrin and use DEET

Thank you!