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VALLEY FEVER IS DIAGNOSED SLOWLY OR NOT AT ALL IN ARIZONA

Donovan, Fariba[1,2] Wightman, Patrick[3], Majeed, Aneela[2], Gabe, Luke[2], and Galgiani, John N[1,2].

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INTRODUCTION Approximately 150,000 cases of coccidioidomycosis (Valley Fever) occur in the United States annually. Seventy percent of these cases occur in Arizona. Additionally it has been suggested that 1% of Arizonans seek medical care annually for new Valley Fever infections. The population of Arizona as of 2015 was estimated to be 6.8 million. Of those who contract Valley Fever, 60% are asymptomatic or resolve spontaneously, 30% have mild to severe respiratory symptoms (mimics community acquired pneumonia, CAP) and nearly 10% develop disease beyond lungs (disseminated coccidioidomycosis, DCM). In endemic regions, 30% of patients diagnosed with CAP are actually thought to have coccidioidomycosis. Arizona patients very frequently experience many weeks of illness before Valley Fever is correctly diagnosed, because of clinician oversight or testing limitations especially in early disease. This study is focused on measuring the delay in Valley Fever diagnosis and calculating the related costs.

METHODS We utilized the Banner University Health system, electronic medical record (EMR) and selected charts within a 12 month interval for which ICD-9 & ICD-10 codes for coccidioidomycosis were first identified. The encounter data for these patients was extracted from the University of Arizona (UA) Health Sciences Clinical Data Warehouse by the UA Center for Biomedical Informatics & Biostatistics – Department of Biomedical Informatics Services. The charts with initial criteria were independently reviewed by two physicians with >98% agreement. We excluded records with i) either mistaken coding, ii) prior coccidioidal infection that was missed in the initial selection, iii) not confirmed by laboratory tests, or iv) pediatric patients. We calculated the time interval from first medical evaluation of syndromes to diagnosis and applied a cost analysis to that interval. Outpatient costs calculated using Medicare Fee Schedules and for inpatient costs California per diem (Sondermeyer, EID 2013) was used.

RESULTS 360 charts met the initial criteria to be reviewed. Of those charts 142 (40%) ultimately met all criteria to be included in the study. The results showed 31% of cases with a delay in diagnosis of greater than 30 days. Median (total) costs for outpatient were $1,400 ($148,944). The inpatient total cost was $367,200. The overall estimated cost before diagnosis was approximately $3,634 per patient.

CONCLUSION We have demonstrated significant delays and associated costs with a slower diagnosis of Valley Fever in this endemic area. Projecting back to the 150,000 annual cases in the United States emphasizes the need to improve and speed the earlier diagnosis of Valley Fever. This will alleviate patient suffering, morbidity and reduce costs to an overburdened healthcare system. As will be discussed, analyzing costs associated with this delay in an otherwise straightforward study has been challenging.

TESTING FOR COCCIDIOIDOMYCOSIS IN EMERGENCY DEPARTMENTS IN ARIZONA

Khan Mohammed[1,2], Brady Shane[1], Adame Guillermo[1], Komatsu Ken[1]

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[2]Laney Graduate School and Rollins School of Public Health, Emory University, Atlanta, GA

Introduction

Testing practices for coccidioidomycosis in the emergency department (ED) are not well understood. Some studies have suggested that coccidioidomycosis may be a common cause of community-acquired pneumonia (CAP) in Arizona and testing for coccidioidomycosis is uncommon in such patients. We describe characteristics of patients tested for coccidioidomycosis in EDs, trends in testing, and coccidioidomycosis testing among CAP patients in Arizona.

Methods

Testing provider and facility information, as well as ED visit records with admission dates between 1/1/2014 and 12/31/2016 were extracted from the Arizona hospital discharge database. Only records from adult Arizona residents with Current Procedural Terminology (CPT) codes for coccidioidomycosis testing were included. We also compiled a separate sample of patients with ED visits associated with CAP between 1/1/2014 and 12/31/2014. We defined CAP using ICD-9-CM discharge diagnosis codes for pneumonia due to infection. Exclusion criteria for this sample included patients who were not admitted from the community, were hospitalized in the 90 days prior to their ED visit, or were previously reported coccidioidomycosis cases. Only records with CPT codes for chest x-ray were included. Analyses were performed in SAS v9.4.

Results

In 2014, there were 2,672 ED visits with a CPT code for coccidioidomycosis testing. Excluding asthma with acute exacerbation (3.4%) and influenza (2.2%), the top 50% of principal discharge diagnoses reflected symptoms and syndromes consistent with primary pulmonary coccidioidomycosis. Sixty-one (10.3%) of 603 providers and five (8.9%) of 56 healthcare facilities accounted for half of all patients tested for coccidioidomycosis in the ED. Approximately one-third of all patients were tested at a single facility. There were 13,294 ED visits associated with CAP included in the analysis. The most common CAP-defining ICD-9-CM codes were pneumonia, organism unspecified (73.2%) and influenza (24.2%). Overall, 371 (2.8%) visits had a CPT code for coccidioidomycosis.

Conclusion

Our analysis demonstrated that coccidioidomycosis testing varied substantially by facility and provider. A small number of facilities and providers accounted for a disproportionate number of tested patients. More insight into clinical decision making regarding coccidioidomycosis testing in ED's is needed.

CHALLENGES IN COCCIDIOIDOMYCOSIS SURVEILLANCE IN WAHINGTON STATE: PROVIDER AWARENESS AND LABORTATORY REPORTING

Oltean HN, Hubber J, Fuller M

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Introduction

The epidemiology of coccidioidomycosis in Washington is not completely understood. Under-recognition and under-reporting of coccidioidomycosis is suspected based on reports of only severe disease. Disease surveillance relies on clinical awareness and clinician and laboratory reporting to public health. Enhanced surveillance efforts to better understand barriers to diagnosing and reporting disease cases to public health are underway. Two of these efforts, a knowledge, attitudes, and practices (KAP) survey among healthcare providers, and a review of commercial laboratory data, are assisting in understanding these barriers.

Methods

To assess healthcare provider awareness, we conducted an online, self-administered KAP survey from February – April 2017 in south-central WA, representing a region thought to be endemic for the *Coccidioides* fungus. To evaluate our laboratory-based surveillance system, we requested positive and negative results for laboratory tests specific to coccidioidomycosis from nine laboratories performing testing for Washington State residents during 2012-2015. We compared these results with cases of coccidioidomycosis reported to the Washington State Public Health Issue Management System (PHIMS).

Results

The majority of KAP survey respondents were unaware of the reporting requirement for coccidioidomycosis in WA, and further unaware that the disease had been reported in the state. Less than a third of survey respondents reported confidence in their ability to diagnose coccidioidomycosis, and the majority never or rarely consider a diagnosis of coccidioidomycosis in their patients. Previous education, training, or practice with coccidioidomycosis was the only identified predictor of confidence and consideration of risk. The commercial laboratory assessment identified 4,038 Washington State residents tested for coccidioidomycosis from 2012 to 2015. Of these tested individuals, 227 (5.6%) had at least one positive test result. Disease reporting was first requested by the Washington State Department of Health in April 2014; reporting increased from 9.2% pre-April 2014 to 28.8% post-April 2014.

Conclusion

These data indicate the enormous need for education and training among healthcare providers in south-central WA, and support the concern that a small proportion of existing cases of coccidioidomycosis are reported to the health department. Reporting has increased over time, but significant gaps remain. Healthcare provider awareness and expertise, as well as complete reporting from clinicians and laboratories are necessary to improve the epidemiological understanding of this emerging condition in WA.

COCCIDIOIDOMYCOSIS CASES WITH PERSISTENTLY POSITIVE TEST RESULTS

Khan Mohammed[1,2], Brady Shane[1], Adame Guillermo[1,] Komatsu Ken[1]

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[2]Laney Graduate School and Rollins School of Public Health, Emory University, Atlanta, GA

Introduction

In Arizona, all positive *Coccidioides* test results are reportable to the state health department. Long-term laboratory characteristics of reported coccidioidomycosis in Arizona have not been analyzed. We described the characteristics of patients with positive test results one year or more after the first positive test.

Methods

Demographic and laboratory data for confirmed coccidioidomycosis cases reported to the Arizona Department of Health Services between 2013 and 2015 were obtained from the state surveillance system. Patients with a positive test result at least one year after the collection date of the initial positive *Coccidoides* test were included in the analysis. Laboratory results for specimens collected up to two years after the first laboratory test were included. Laboratory results were analyzed using a SAS-based string matching algorithm. Patients were grouped and analyzed by test type of the positive test result one year or more after the initial positive test. Descriptive statistics were calculated in SAS v9.4.

Results

There were 19,045 confirmed cases reported during the study period of which 18,379 (96.5%) were available for analysis. We identified 1,498 (8.2%) patients with positive *Coccidioides* test results one year or more after the first positive test. Of these, 131 (8.7%) patients had positive culture/histopathology results at least one year after initial positive test; 623 (41.6%) had positive complement fixation results; 603 (40.3%) had positive immunodiffusion results; 968 (64.6%) had positive EIA IgG results; 277 (18.5%) had positive EIA IgM results. Ninety seven (6.5%) patients had a higher complement fixation titer one year or more after the initial positive complement fixation test. A mean of 554 days elapsed between the first and last positive tests. Demographic characteristics varied by laboratory test results. Patients in nearly all subgroups were more likely to be male, ranging from 56.0% of EIA IgG positive patients to 69.5% of culture positive patients, with the exception of EIA IgM positive patients (45.1% male). Immunodiffusion positive patients had a higher mean age than all other subgroups (54 vs. 50 years).

Conclusion

Further study of these patients, including medical record review to collect clinical characteristics, may provide insight into healthcare provider laboratory testing practices, follow-up of coccidioidomycosis patients, and the burden of severe or chronic coccidioidomycosis.

ENHANCED SURVEILLANCE OF COCCIDIOIDOMYCOSIS IN SAN DIEGO COUNTY, 2014-2016

Arizmendi, Olivia[2]; Fabian, Eva[1]; Balagot, Caroline[2]; Iniguez-Stevens, Esmeralda[2]; Kao, Annie[1]

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Introduction

Coccidioidomycosis (Valley Fever) is a respiratory infection caused by Coccidioides immitis or Coccidioides posadasii. These pathogenic fungi thrive in desert regions such as those in the southwestern region of the US. The County of San Diego, CA is an area with the environmental, demographic, and occupational settings associated with the dissemination of coccidioidomycosis. Therefore, the California Border Infectious Disease Surveillance Program conducted enhanced surveillance of coccidioidomycosis in order to further the knowledge of the disease in this region.

Methods

A questionnaire detailing symptoms, occupational and travel exposures was administered to confirmed coccidioidomycosis cases in San Diego County. Medical and laboratory data were used to categorize cases as acute or chronic. The geographical distribution of cases was determined with ArcGIS. Descriptive statistics were evaluated with SAS 9.4.

Results

Of the cases identified (n=337) via enhanced surveillance, 48% were acute (n=161), 24% were chronic (n=80), and 28% were chronic cases among inmates (n=96). Seventy-five percent were male (n=254). Sixty-one percent (n=131) specified ethnicity; of those, 42% were Hispanic (n=86). Dissemination to bones, joints, and organs occurred in 25 cases. Acute cases indicated they sought care approximately one month after symptom onset (mean=26.4, median=9.5 days). Acute cases occurred at a rate of 4.2 per 100,000 in San Diego County, with the highest rate of 11.9 per 100,000 cases in the South Suburban area of the county.

Conclusion

The residents of San Diego County are at an elevated risk of coccidioidomycosis due to the environmental features of the region. Enhanced surveillance of coccidioidomycosis cases showed there were delays in seeking care among acute cases. Additionally, the south region of the county had a higher rate of cases reported. These results warrant further examination into the factors that could be determining the increasing rates of coccidioidomycosis in California.

RECENT TRENDS IN COCCIDIOIDOMYCOSIS IN THE DEPARTMENT OF VETERANS AFFAIRS (VA)

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[2]Div. of Infectious Diseases & Geographic Medicine, Stanford, CA

Introduction

The incidence of coccidioidomycosis (CM) has increased in recent years, but little is known about CM in Veterans. Herein, we describe recent trends in CM outpatient visits, hospitalizations and laboratory testing in national VA data from Jan 2010-May 2017.

Methods

CM hospitalizations, outpatient visits, and laboratory data (serology, immunodiffusion, complement fixation and cultures) were obtained from VA data warehouses. Data extracted included demographics, location, diagnosis codes, laboratory results, treatment, encounter details and deaths during CM-coded hospitalizations.

Results

Encounter data review identified 4,523 unique Veteran patients with 24,415 outpatient visits and 1,916 hospitalizations. Median age was 63 years (range 20-95), and 93% (4,228) were male. Over 76% (3,447) resided in the West US Census region, with the top counties being Maricopa, AZ (769), Pima, AZ (712), Los Angeles, CA (242), Pinal, AZ (159), and Kern, CA (113). CM was the principal diagnosis for 342 (18%) of CM-coded hospitalizations. Median length of stay was

5 days, with 318 (17%) spending time in intensive care and 89 deaths (5%). In 500 patients with meningitis or disseminated CM, 84% received antifungal(s) [including fluconazole (72%), itraconazole (14%) and voriconazole (11%)] and a higher percentage were African American and Asian compared to overall Veteran CM patients. Types of CM recorded are presented in Table 1. Trends in inpatient, outpatient, and non-culture based laboratory testing for CM are shown in Figure 1.

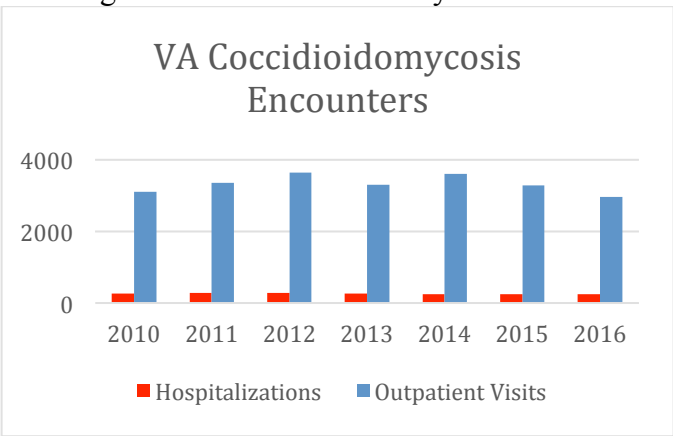
Conclusion

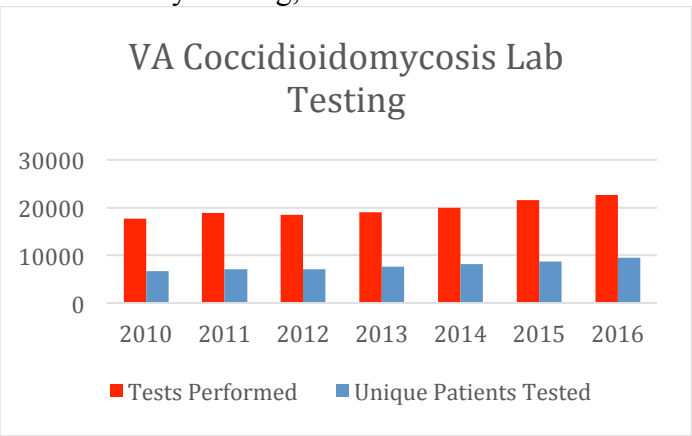
CM causes substantial morbidity and mortality in Veterans with cases occurring primarily in AZ and CA. The number of VA encounters coded with CM has remained relatively stable over the last 7 years, although testing for CM has increased.

Table 1. VA Coccidioidomycosis (CM) Encounter Details, Jan. 2010- May 2017

	Hospitalizations N=1,916	Unique Inpatients N=1,202	Outpatient Visits N=24,415	Unique Outpatients N=3,981
Types of CM, N (%)				
Pulmonary	901 (47)	552 (46)	8,682 (36)	1,584 (40)
Primary pulmonary	311 (16)	232 (19)	3,264 (13)	627 (16)
Disseminated/Progressive	262 (14)	129 (11)	2,259 (9)	141 (4)
Meningitis	137 (7)	50 (4)	1,369 (6)	77 (2)
Primary extrapulmonary	25 (1)	18 (1)	464 (2)	93 (2)
Unspecified	635 (33)	479 (21)	12,052 (49)	2,125 (53)

Figure 1. VA Coccidioidomycosis Encounters and Laboratory Testing, 2010-2016





DIRECT DETECTION OF *COCCIDIOIDES* FROM AIR SAMPLES IN PHOENIX, AZ

Gade, Lalitha[1]; Bowers, Jolene R[3]; McCotter, Orion[1]; Komatsu, Kenneth[2]; Waddell, Victor[2]; Carvajal, Joseph[2]; Brady, Shane[2]; Sunenshine, Rebecca[4,5]; Engelthaler, David M[3]; Chiller,Tom[1], Litvintseva, Anastasia P.
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Introduction Environmental surveillance of airborne *Coccidioides can be used to* address many relevant questions about epidemiology of coccidioidomycosis. However, the detection of this pathogen in ambient air has historically been very difficult and has a very low success rate. In this study, we sought to develop and validate a novel approach for detection of airborne *Coccidioides* arthroconidia directly from ambient air samples and used this method to investigate the temporal and spatial distribution of arthroconidia in air samples collected from multiple locations around Phoenix metropolitan area, Arizona over 48 days.
Methods In this study, 831 air samples were collected using portable air sampling units with a sampling flow rate of 100 liters per minute; one filter was collected every 24 hours. Of those, 63 air filters were collected from 21 sites during large dust storms from August 24 to 26, 2015 and 768 air filters were collected from 17 sites from September 24 to November 10, 2016. Large dust storms were active on the evenings of September 27, 2016 and October 15, 2016 in the Phoenix area. Genomic DNA was extracted directly from Polytetrafluoroethylene (PTFE) air filters using the PowerLyzer Power- Soil DNA Isolation Kit (MO BIO Laboratories, Inc.; Carlsbad, CA, USA) and tested using a previously established single-tube nested qPCR assay. In addition, the samples were tested with the newly developed CocciEnv assay for detection of *Coccidioides* in the environment and the amplification products were prepared and quantified using the Library Quantification Kit (KAPA Biosystems) and sequenced in 2x300 mode on an Illumina MiSeq Desktop Sequencer. To determine the limit of detection, known concentrations of laboratory-purified arthroconidia were spiked on PTFE filters and processed.
Results When blank filters were spiked with known concentrations of arthroconidia, the method was capable of detecting one arthroconidium per filter. Comparable results were obtained using single-tube nested qPCR, and CocciEnv assays. Of the air samples collected during the August 24-26, 2015, dust storms, a larger proportion of air samples were positive for *Coccidioides* on the day prior to the dust storm (17 of 21, 62%) compared to those collected during the storm (4 of 21, 19%). Of the air samples collected from 17 sampling sites from September 24 to November 10, 2016, *Coccidioides* was detected consistently from two sites, while the rest of the sites were either sporadically positive certain days or negative. Specifically, 23 of 45 (51%) samples from site A and 29 of 45 (64%) of samples from site B were positive for *Coccidioides*, and no *Coccidioides* DNA was detected from any of the 45 samples from site C. From the rest of the sites, *Coccidioides* was detected in 1-5 samples.
Conclusion In this report, we demonstrated that our novel method of detection of *Coccidioides* in ambient air is a promising technology that can be used to address many important questions about coccidioidomycosis epidemiology. Preliminary testing results of samples collected from 17 different sites over 48 days suggest uneven distribution of *Coccidioides* in the air. Although *Coccidioides* was detected in 16 sites, two sites were consistently positive suggesting presence of *Coccidioides* hot spots. No correlation of *Coccidioides* and dust storms has been found but more testing is needed.

DETERMINING OCCCUPATIONAL CAUSATION OF COCCIOIDOMYCOSIS - TWO CASE STUDIES

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Introduction

Coccidioidomycosis cases are known to occur in a variety of occupational settings that involve disturbing soil in areas endemic for the fungus. Securing compensation for medical expenses and lost work time, and justifying regulatory actions by public health and safety agencies, often involves being required to prove in administrative or Court proceedings that spore exposure was due to job activities. Where a group of workers is exposed and multiple cases occur, a traditional argument is that the individual was a member of a group that experienced a substantially elevated incidence rate relative to the background population incidence rate. However, where a single worker develops Coccidioidomycosis and information about the health experience of coworkers is not available, group incidence rates cannot be compared. An alternative approach is to compare the cumulative soil dust exposure (mg-hour/m^3) experienced on the work site versus experienced away from the work site.

Methods and Results

A case study is used to illustrate each approach. The first involves seven cases of severe pneumonia among a crew of ten highway construction workers that occurred in Kern County in 2008. Given the short exposure period (four to seven work days over two calendar weeks), it is shown that the probability the cases arose due to the background infection risk was less than one in 10^{18}. Contributing factors were that the contractor was not informed of the infection risk and did not take adequate precautions against soil dust exposure. The second case study involves severe pneumonia in a single worker who operated heavy equipment on an oil field in Kern County during a one-month period in 2016. No health information was available about coworkers. The individual's tasks created heavy dust exposure for which he had inadequate respiratory protection. Off the oil field, the worker resided in a hotel about 40 miles away. Based on estimates of the respirable soil dust exposure levels while performing the tasks versus staying in the hotel and commuting, it was estimated that cumulative occupational soil dust exposure was at least 19-fold greater than cumulative background soil dust exposure.

Conclusion

In both case incidents, causation was deemed work-related by independent medical-legal examiners. Necessary exposure reduction measures are discussed.

COCCIDIOIDOMYCOSIS AMONG WORKERS CONSTRUCTING A SOLAR POWER FARM IN MONTEREY COUNTY, CALIFORNIA, 2016-2017

Rebecca L. Laws[1,2], Gail Sondermeyer Cooksey[1], Seema Jain[1], Jason Wilken[1,2], Jennifer McNary[1], Edward Moreno[3], Kristy Michie[3], Christy Mulkerin[4], Ann McDowell[4], Duc Vugia [1], Barbara Materna[1]

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Background

Coccidioidomycosis is an infection resulting from inhalation of spores of the soil-dwelling fungus *Coccidioides*. Workers performing at or near soil-disturbing activities in endemic areas are at risk. In January 2017, two county health departments notified the California Department of Public Health of coccidioidomycosis cases among workers constructing a solar farm in Monterey County and requested assistance.

Methods

We matched solar farm employee rosters during February 2016–April 2017 with the California Reportable Disease Information Exchange database for case-finding, and we conducted worker interviews. Cases had clinical and laboratory-confirmed coccidioidomycosis, with illness onset ≥1 week after beginning work and <1 month after final solar farm workday. We calculated incidence rates among workers by dividing number of cases by total person-years spent at the worksite, and compared these rates with incidence rates for Monterey and surrounding counties.

Results

Among 2,410 employees, we identified 9 cases. Median age was 42 years (range: 20–63 years); 7 were male; all were previously healthy. Five visited emergency departments; 1 was hospitalized and none died. Construction began June 2016; illness onset dates were August–December 2016. Of the 8 patients interviewed, 7 worked only at the solar farm within 4 weeks before illness onset; 1 also worked elsewhere. Seven patients missed work because of illness (median: 14 days; range: 1–320). Patients reported dusty work conditions, an inadequate respiratory protection program, and minimal coccidioidomycosis training. Annual coccidioidomycosis incidence among workers was 1170.5/100,000 persons; the 2016 incidence for Monterey and surrounding counties ranged from 2.9–157.3/100,000 persons.

Conclusion

The disproportionately high infection rate among workers indicates coccidioidomycosis was likely acquired at work. To prevent additional cases during future construction, we recommended improved dust control, respiratory protection, worker training, and illness tracking and reporting. These recommendations have implications for employers and health care providers when construction projects occur in *Coccidioides*-endemic areas.

COCCIDIOIDOMYCOSIS AMONG INMATE WILDLAND FIREFIGHTERS IN CALIFORNIA, 2017

Rebecca L. Laws[1,2], Janet Mohle-Boetani[3], Seema Jain[1], Gail Sondermeyer Cooksey[1], Bruce Leistikow[3], Jason Wilken[1,2], Jennifer McNary[1], Duc Vugia[1], Robert Harrison[1], Barbara Materna[1]

[1]California Department of Public Health, [2]Centers for Disease Control and Prevention
[3]California Correctional Health Care Services

Background

Coccidioidomycosis is a disease resulting from inhalation of spores of the soil-dwelling fungus *Coccidioides*. In August, 2017, the California Correctional Health Care Services and the California Department of Public Health investigated five laboratory-confirmed coccidioidomycosis cases among inmate wildland firefighters who worked on a 4-day fire in California's Central Valley (*Coccidioides*-endemic area).

Methods

We mailed surveys to inmates deployed to the wildfire for additional case-finding and to assess symptoms, job tasks, prevention measures, and training. We reviewed medical records when available. We defined a case as laboratory-confirmed or clinical coccidioidomycosis (reporting ≥1 respiratory and ≥1 systemic symptom), with illness onset ≥1 week after the fire started and <1 month after the fire ended. Control subjects reported no symptoms. We used age-adjusted logistic regression to assess associations between risk factors and coccidioidomycosis.

Results

All 198 deployed inmates were male. Among 174 inmates with available mailing addresses, 112 (64%) responded to the survey. Median age was 30 years (range: 19–52 years). Five clinical cases were identified by survey totaling 10 case-patients. One of these cases reported laboratory-confirmed diagnosis, which was confirmed via medical record. Two case-patients were hospitalized for respiratory failure and meningitis. Sixty-one respondents reported no symptoms and were classified as control subjects. Thirteen did not respond to symptoms questions, one was excluded for previous coccidioidomycosis diagnosis, and 27 were symptomatic non-cases who reported some symptoms but did not meet the case definition. Compared with control subjects, case-patients were more likely to report frequently being in a dust cloud (odds ratio [OR]: 4.3; 95% confidence interval [CI]: 1.1–17.5); cutting fire line with a rake (OR: 5.7; CI: 1.3–25.5); and tossing dirt in the air (OR: 5.1; CI: 1.1–23.2). Among respondents, 90% reported never receiving coccidioidomycosis training, 94% reported never wearing respiratory protection on any fire, and 100% reported not receiving respirator fit-testing.

Conclusion

Inmate firefighters exposed to soil dust in *Coccidioides*-endemic areas are at risk for disease. Agencies deploying inmate firefighters to these areas should train them about coccidioidomycosis symptoms and risk reduction, limit dust exposure, and implement respiratory protection programs.

SCIENTIFIC MEETING **April 14, 2018**

Continental Breakfast/Registration

Welcome and Announcements - Neil Ampel

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POSTER Presentations

The Program Committee, Moderators

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SMALL MOLECULE SCREENING OF EUKARYOTIC RECOMBINANT ENDOCHITINASE-1 IN *COCCIDIOIDES POSADASII*

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Introduction

Chitin biosynthesis has long been an attractive target for anti-fungal therapeutic development. *Coccidioides posadasii* is sensitive to Nikkomycin Z, a promising chitin synthase (CHS) inhibitor that is thought to competitively inhibit CHS due to structural similarity of NikZ to CHS substrate, UPD-GlcNAc. NikZ is currently undergoing phase II clinical trials, and preliminary data suggests anti-fungal activity as insufficient for the treatment of severe disease. Currently, there are no available treatments that specifically target chitinase enzymes, thus, the search for a *Coccidioides*-specific small molecule inhibitor with fungicidal activity continues.

This project aims to ultimately explore the hypothesis that targeting CTS and CHS in *Coccidioides spp*. attenuates growth of the fungus *in vivo*. We produced eukaryotic recombinant CTS enzymes and established a screening assay for potential inhibitors.

Methods

Coccidioides posadasii endochitinase-1, also known as CF-chitinase or CTS1, was successfully cloned and expressed in a eukaryotic system (eukaryotic recombinant CTS1, E-rCTS1). CTS1 was assembled by PCR splicing, cloned, sequenced, and expressed from mammalian expression vector pcDNA3.1/V5-HisA in HEK-293F cells. Recombinant protein was purified via affinity chromatography Ni/NTA column.

Purified E-rCTS1 was characterized via chitinase assay, in which hydrolytic activity of E-rCTS1 was measured relative to the amount of p-nitrophenol cleaved from nitrophenol-labeled substrates. This assay was used to screen enzymatically active E-rCTS1 against a small molecule library of known anti-fungal compounds. E-rCTS1 was incubated with 50 uM small molecule, then tested for inhibition of enzymatic function. The principle of the assay is based on signal attenuation when CTS1 is inhibited.

Results

Using the chitinase assay described in methods, we screened E-rCTS1 against the Targetmol anti-fungal compound library. The assay identified caffeine as a dose-dependent inhibitor of CTS1, active in the low mM range. Additionally, known anti-fungal compound dequalinium chloride exhibited inhibitory activity comparable to caffeine.

Conclusion

Production of recombinant chitin-remodeling enzymes expressed in a eukaryotic host provides a biologically relevant target to be used in the search for new anti-fungal therapeutics. Ongoing work in our lab includes production of additional targets, as well as further screening of recombinant targets against small molecule libraries.

DETERMINING THE AMOUNT OF *COCCIDIOIDES* PRESENT IN A SOIL SAMPLE BASED ON QUANTITATIVE PCR ANAYLSIS

Daniel Kollath, Bridget Barker

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Introduction

There is a knowledge gap regarding the ecology of *Coccidioides posadasii,* the causative agent of the disease Valley Fever. The factors that determine where the fungus can persist in the soil are not well understood. The effect of soil characteristics (e.g. texture, pH, carbon profile, nitrogen, etc.) on growth is also poorly understood. Tracking the organism in the soil is one way to improve disease surveillance but there is not a standard detection method among *Coccidioides* researchers. When using real time-qPCR to detect the fungus in soil it is difficult to quantitatively determine the amount of fungal cells present in a sample. This study examines how many fungal cells inoculated into sterile soil correspond to *Coccidioides* DNA detected using a recently published assay. We determined the amount of *Coccidioides* arthroconidia present in a soil sample by comparing qPCR cycle threshold values to known concentrations of arthroconidia that have been inoculated into a soil sample. We hypothesize that higher concentrations of conidia will result in lower cycle threshold values.

Methods

Soils from four different sites in Arizona were sterilized two times. One quarter (0.25) gram samples were inoculated with dilutions of *Coccidioides* arthroconida beginning at 10^6 cells per milliliter to 10^2 cells per milliliter. Soil was allowed to rest for 6 days before DNA extraction. DNA was extracted using Qiagen DNeasy Power Soil kit. DNA was amplified using FungiQuant and CocciENV assays.

Results

We examined the relationship between the amount of conidia in a soil sample and Ct value. The higher conidia concentration produced lower Ct values. We also examined that abiotic soil factors were not significantly different between sites.

Conclusion

This study helps researchers who are trying to detect *Coccidioides* in the soil approximate how many fungal cells are in the soil sample based on Ct values. This type of information can help answer one of the many ecological questions about this organism. It also shows that the soil may not be a driving force that determines where the organism is in the environment, though more investigation is needed, and there are other factors such as reservoirs.

COCCIDIOIDOMYCOSIS IN *CANIS LUPUS FAMILIARIS*

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Introduction

Valley Fever Prevention Awareness and Working for Solutions (PAWS) Project is a project focused on understanding host specific contribution to coccidioidomycosis, also known as valley fever, by looking at the disease in dogs and the canine genome. Valley fever is a fungal infection caused by *Coccidioides sp.* found in the southwestern United States, Mexico and South America. The Valley Fever PAWS project is an online survey open to any dog owner. The survey requests information on whether any of their dogs have been diagnosed with valley fever and a few demographics about the dog. Questions include sex, age, breed, location of residence, if the dog is house bound, how often the dog is the walked, if the dog is a companion in camping/hiking, and a section is included for dog owners to comment if the dog engages in other outdoor activities. The data from the survey is placed in a database in which the data is analyzed for any correlations amongst the dogs from the survey and how the mycosis is presented in a certain demographic. Currently, the effect of breed on the rate of infection is the project's focus.

Methods

The top twenty breeds represented in the survey were determined, and the Chi-square test performed to determine any breeds that were significantly different from the average rate of disease. The average rate of disease was determined using the ratio of self-reported cases to the total number of dogs enrolled in our study. Saliva was collected using Genotek Performagene™ (PG-100) kits by the dog owners. DNA was extracted using the "Laboratory protocol for manual purification of DNA" from 0.5 mL of Performagene™ sample by Genotek protocol.

Results

The expected average of infection for dogs is 30%, although amongst breeds that number varies. The database has 2682 participants 131 breeds, 907 infected dogs, and 1775 :healthy dogs. Four breeds were determined to be significantly different from the average rate of infection. Boxers, Golden Retrievers, and Yorkshire Terriers all have a higher susceptibility rate to the mycosis while Chihuahuas are the only breed that has a lower susceptibility rate. Two breeds of particular interest are Boxers and Chihuahuas for their significantly higher and lower rates of disease, respectively. Of the 131 Boxers in the database, fifty-five were infected. Of 119 Chihuahuas, twenty-two were infected. DNA extractions were performed on thirty-eight Boxer saliva samples and twenty-eight Chihuahua saliva samples. Twelve healthy and twelve infected Boxer samples were sent to TGen Headquarters to be sequenced.

Conclusion

These results provide evidence of breed and hence host factors contributing to the mycosis. More investigation is needed to examine this such as running the SNP genotyping array on the twenty-four Boxer samples and analyzing the preliminary data for any correlation between the genome of the breed and disease susceptibility. To further investigate would require to genotype Chihuahuas, a breed with a significantly lower rate of infection to further understand the host contributions in valley fever.

LARGE-SCALE *COCCIDIOIDES* SOIL SAMPLING METHOD

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Introduction

Coccidioides spp. are soil-borne fungi that cause coccidioidomycosis, the disease known as Valley Fever. The ecological niche of this fungus is not understood. However, soil samples from rodent burrow entrances, previous positives, areas where dogs or humans have been diagnosed, and places where animals that had Valley Fever are buried, often provide positives. Going to arid regions randomly does not yield consistent results. For our study we wanted to complete a transect at Bunyan Wash (Tuscon, AZ), a site that has been consistently positive since 2014, and see how far spread the *Coccidioides spp*. can be detected from our central positive location. The purpose of this study was to organize an efficient large-scale soil collection method for *C. posadasii*. to enhance our knowledge on the ecology of the organism and lead to better disease surveillance. When conducting a large-scale soil collection, specific measurements need to be documented so that the exact location can be found again and re-sampled.

Methods

Bunyan Wash, a site that is believed to be positive from previous sampling, is where this study was conducted. This site has very dry soil due to the arid environment and an abundance of rodent burrows that appear to be more clustered under the desert vegetation. Two topsoil samples were collected by going 5 meters out from a central location (previously positive site) in every cardinal and intermediate direction. Every cardinal and intermediate direction was marked with a flag. Samples were collected using a sterilized hand shovel and placed into sterilized collection cups. Soil was also sampled from every rodent burrow within the 5-meter and 10-meter circumference. DNA samples were extracted from the soil using a Qiagen DNeasy Powersoil Kit (using the manufacturer protocol) and was then analyzed with rt-qPCR using the CocciENV assay.

Results

From this study we were able to establish a standardized soil collection method for detecting and monitoring an existing *C. posadasii* colony in the environment. In total, 71 sample cups were collected. So far 30 DNA evaluations from 1 topsoil sample and 2 rodent burrows samples within a range of 5-meters were evaluated. All qPCR reactions using the CocciENV assay approach have so far come out negative.

Discussion

Environmental studies of *Coccidioides spp*. are scarce, and the ecology of the fungus is not completely understood. Organizing a more efficient sampling method will contribute to the ecological studies by identifying and monitoring the presence of the fungus in its proposed natural environment (burrows) as compared to topsoil.

HEAT TREATMENT TO INACTIVATE RISK GROUP 3 *COCCIDIOIDES SPP.*

Blackmon Austin, Mead Heather, Vogler Amy, Barker Bridget

Pathogen and Microbiome Institute, Northern Arizona University

Introduction

Coccidioides spp. is a fungal pathogen that causes the disease commonly called Valley Fever. This endemic disease is caused by two recently classified *Coccidioides* species: *C. immitis* is found in California, Eastern Washington and Mexico, while *C. posadasii* is widely distributed in Arizona, Texas, Mexico, and South and Central America. Both species of *Coccidioides* are categorized as Risk Group 3 (RG3) and need to be worked with inside Biosafety Level 3 (BSL3) facilities. Working in a BSL3 is time intensive, costly, and requires special training. Often *Coccidioides* DNA is desired for genomic studies and must be extracted in the BSL3 setting. Filamentous fungal DNA is difficult to extract due to resilient cell walls, and this limits the functionality of commercial extraction kits, which do not yield high amounts of DNA. Extractions that yield both high quality and quantity DNA require the use of phenol/chloroform protocols. While this method is more effective in overall DNA yield the chemical hazards and lengthy protocol are burdensome in a BSL3 laboratory. We propose to address these issues by heat inactivating *Coccidioides* species so that phenol chloroform DNA extractions can occur in a BSL2 setting.

Methods

To determine appropriate inactivation conditions mycelia and arthroconidia from *C. immitis* strain RS and *C. posadasii* strain C735 were subjected to a series of temperatures and times. Viable cells were placed in a heat block at time points 1, 2, 5, 10, 20, and 30 minutes at 80 °C to develop an exposure kill curve. Both species were placed in a heat block at time points 65, 70, and 75 °C for 10 minutes for arthroconidia and 30 minutes for mycelia. The inactivated fungal samples along with positive controls were plated on 2xGYE and incubated at 30 °C for 2 weeks to ensure inactivation. DNA extractions of both live and inactivated cells were performed according to a protocol developed by Bridget Barker.

Results

Mycelia for both C735 and RS were effectively killed at 80°C for 30 minutes and for arthroconidia 80°C for 10 minutes. The inactivated plates of fungal samples along with positive controls were checked after 2 weeks of incubation and found to have no growth. Phenol chloroform DNA extractions were performed on live and heat inactivated mycelia. DNA integrity and amount were inspected using 0.8% gel electrophoresis. Both sample types had a concentration of approximately 38.8 ng/ul of DNA.

Conclusion

This heat kill protocol reduces the time to extract fungal DNA by 64% and is less costly than performing the extraction entirely in the BSL3. Overall quality and quantity of the DNA was not impacted by the inactivation procedure. This reduces the time spent in the BSL3 laboratory and allows research associates who are not trained in the BSL3 to complete DNA extractions in a BSL2 protocol.

EXPLORING EOSINOPHILIA: A CASE OF COCCIDIOIDOMYCOSIS AND STRONGYLOIDIASIS CO-INFECTION

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Background

Coccidioides immitis, a dimorphic, soil dwelling fungus is found endemic in the southwestern United States. Approximately 65% of all valley fever cases occur in Arizona, and and 30% occur in California. Strongyloidiasis is a human parasitic infection caused by the nematode *S. stercoralis*. Strongyloidiasis is found in central and South America, sub-Saharan Africa and southeast Asia. Cases diagnosed in the United States are found in people who have lived or traveled in endemic areas.

Case Summary

This case presentation is that of a 26 year old male with remote travel to Jamaica. Initial symptoms included a cough followed by a six week history of worsening fatigue. The patient presented with sudden onset of chest pain and shortness of breath. Examination found moderate distress, tachypnea and normal cardiac, abdominal and skin examination.
Initial tests showed an elevated white cell count with eosinophilia, and the chest x-ray revealed a right hydropneumothorax. The initial chest computerized tomography (CT) scan showed a right lung cavity with satellite nodules. The pleural fluid was exudative and grew *Coccidioides* (cocci), while the cocci complement fixation (CF) titer was 1:32. HIV serology was negative, and no immunosuppressive condition was found. A right bronchopleural fistula required right thoracotomy with decortication and debridement and subsequent lobectomy. Therapy included fluconazole until repeat thoracotomy was done. Voriconazole was substituted for fluconazole postoperatively. Pathology showed septated hyphae in the alveoli, and cocci grew in the surgical culture. The lung biopsy showed changes suspicious for *Strongyloides* larvae, but stool specimens were negative. *Strongyloides* serology was positive for IgG, and the patient was treated with ivermectin. The ivermectin resolved the eosinophilia and correlated with further clinical improvement.

Discussion

After literature review this case appears to be the first report of co-infection with *Coccidioides* and *Strongyloides*. Persistent eosinophilia in spite of otherwise effective therapy for cocci encouraged the pursuit for additional causes of pulmonary disease, such as strongyloidiasis. We believe that the patient first acquired *Strongyloides* infection in Jamaica. *Strongyloides* likely reactivated as a pulmonary infection which satisfied the definition of hyperinfection. Recent exposure to cocci after moving to the endemic area (Arizona) resulted in co-infected lung tissue complicated by the rupture of a cocci cavity with a bronchopleural fistula.

DISSEMINATED COCCIDIOIDOMYCOSIS IN THE PRE-AMPHOTERICIN ERA: EXAMINATION OF THE VA-ARMED FORCES DATABASE

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Introduction While it has been previously well described that central nervous system (CNS) coccidioidomycosis is nearly always fatal without treatment, the natural history of non-CNS disseminated coccidioidomycosis (DCM) infections is not well characterized. The historical VA-Armed forces coccidioidomycosis patient group provides a unique cohort of patients not treated with standard antifungals to characterize the natural history of non-CNS DCM.

Methods We conducted a retrospective study of 595 VA-Armed forces coccidioidomycosis patients diagnosed between 1955-1958 and followed to 1966. Cohorts were identified as non-disseminated disease (487 patients), non-CNS DCM (72 patients), and CNS DCM (36). A combination of chi-square analysis, ANOVA, and Kaplan-Meier analyses were used to compare basic demographic information, laboratory data including serologies and complete blood count data, symptom severity, fate of primary infection, and mortality.

Results There were significant differences in the ethnicity between the cohorts with trends towards increased Black and Filipino patients in the disseminated cohorts (p-value <0.001). There were no statistically significant differences in comorbid conditions. Laboratory data demonstrated increased frequency of leukocytosis with and without eosinophilia in the disseminated cohorts (p-value 0.009). There were significant differences in presenting symptoms with more severe symptoms in patients with disseminated disease (p-value 0.006). Primary fate of infection demonstrated decreased rates of chronic pulmonary nodule in DCMs: 38.19% in non-DCM, 13.89% in non-CNS DCM, and 19.44% in CNS DCM (p-value <0.001). In addition, there were decreased rates of chronic cavities in DCM: 33.26% in non-DCM, 8.33% in non-CNS DCM, and 8.33% in CNS DCM (p-value <0.001). Forty-five percent and 53% of patients in the non-CNS DCM and CNS DCM cohorts, respectively, developed dissemination with initial infection. Mortality at last known follow up due to coccidioidomycosis was significantly different across the cohorts: 1.03% in non-DCM, 15.28% in non-CNS DCM, and 77.78% in CNS DCM (p-value <0.001).

Conclusion This large retrospective cohort study helps further characterize the natural history of non-CNS DCM in comparison to CNS DCM in a population that was not treated with conventional antifungal therapy. While not as fatal as CNS DCM, non-CNS DCM shares many characteristics and has a high associated morbidity.

A CASE OF COCCIDIOIDOMYCOSIS DISSEMINATED TO THE KIDNEY

Coleman, Jeffrey, Heidari, Arash, Hillyer, Shabab

Kern Medical, Bakersfield CA and UCLA David Geffin School of Medicine

Introduction

Coccidioidomycosis (cocci) a predominantly pulmonary disease caused by *Coccidioides spp.,* a dimorphic fungus endemic to Southwest US. In less than 5% of cases it can become disseminated, which complicates the course and prolongs the treatment. We are describing a unique form of dissemination to the parenchyma of kidney with abscess formation. In our experience and review of the literature this has never been reported before.

Methods

This case type was compared to retrospective chart review at Kern Medical.

Results

This is a 56 year old Male oil field worker from the San Joaquin Valley in California. Four years ago he was first diagnosed with pulmonary cocci. At that time his cocci complement fixation (CF) titer was 1:128. He was treated with 3 months of fluconazole and followed off therapy. Two years later he was hospitalized and diagnosed with new onset of uncontrolled diabetes with HbA1c of 15%. During that admission he was found to have a complicated pneumonia with loculated empyema. The pleural empyema was drained and grew *Strep agalactiae*. His cocci CF titers came back at 1:8. He was again given a short course of fluconazole along with antibiotics and followed off therapy. Two years later he presented to our facility for progressive back pain, fatigue and a 20 lb. weight loss. Abdominal CT showed a 15 x 11 x 16 cm left renal mass with cystic and solid components. He underwent fluoroscopic guided drainage and had 800 ml. of purulent fluid that cultured *Coccidioides immitis*. His cocci CF titers increased to >1:512. He was restarted on 800 mg of fluconazole daily and is being co-managed by the infectious disease and urology services at this time. His pigtail drain has been removed, and he is asymptomatic on therapy.

Conclusion

To the best of our knowledge this is the only reported case of dissemination of coccidioidomycosis to kidney with abscess formation. Duration of therapy is expected to be at least 36 months.

TARGETED SEROLOGICAL SURVEY OF CANINES FOR *COCCIDIOIDES* IN WASHINGTON: A PROOF OF CONCEPT PROJECT

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Introduction

Animals can be sentinels for human disease because they share the same environment with people and may be exposed to the same disease causing agents. Animal studies, compared to human testing, can be less complex and a more economical way to screen for disease causing agents in the environment. This project uses a One Health approach to detect *Coccidioides immitis* in the environment. Canine blood samples were tested for antibodies for this fungal pathogen in Washington State. This surveillance approach gathered data from canines residing within two counties (Benton and Franklin) in south central Washington, where a previous serological survey pilot study detected dogs with antibodies for *Coccidioides*.

Methods

Inclusion criteria are: dogs greater than 1 year of age, any breed or gender, no out-of-state travel to Coccidioides-endemic regions, and preferably restricted to travel only within Washington State. Dogs from seven veterinary clinics located in two counties in south central Washington collected serum as convenience samples for testing by Enzyme Immuno-Assay (EIA) at the Oregon State University Veterinary Diagnostic Laboratory.

Results

Canine serum was collected and evaluated for the presence of *Coccidioides* IgG antibodies by an EIA method validated for use on canine sera by Nancy Chow, CDC. Test results indicate that 18% (31 of 176) of samples were positive for Coccidioides IgG.

Conclusion

Canines are a useful environmental sentinel for *Coccidioides*. From this proof of concept study, we propose to expand the geographic range of targeted serologic testing of resident dogs; follow-up with veterinary epidemiologic investigations to isolate likely areas of exposure; and conduct exposure investigations within the areas of likely exposure.

EXPLORING POSSIBLE ECOLOGICAL NICHES FOR COCCIDIOIDES SPECIES ENDEMIC IN NEW MEXICO

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Introduction

Species in the genus Coccidioides, C. posadasii and C. immitis, are the causative agents for coccidioidomycosis, the disease commonly known as Valley Fever. Coccidioidomycosis is estimated to affect more than 150,000 humans each year and is one of the few fungal diseases to affect otherwise healthy individuals. While progress has been made in the clinical understanding of the disease, little is known of the natural biology.

Methods

Eighteen clinical isolates derived from seventeen individuals diagnosed with coccidioidomycosis collected from New Mexico were used in a multi-locus sequencing analysis to explore genetic variation within the state and between neighboring states. We are also taking a novel approach to screen small rodents for exposure to Coccidioides by two means: 1) a survey of frozen mammal lung tissue for fungal infections, and 2) an enzyme immunoassay that detects IgG antibodies against Coccidioides in a variety of mammalian species.

Results

While New Mexico is predicted to have C. posadasii, results of our multi-gene analysis indicate that both C. immitis and C. posadasii are present among clinical isolates across New Mexico. Five of eight infections for which patient ethnicity was known occurred in Native Americans, suggesting further studies should be conducted to determine if American Indians represent a risk group for coccidioidomycosis.

Conclusion

Characterization of clinical and environmental isolates will allow us to understand the genetic variation that affects the virulence of these pathogens, animal infection rates, the geographical distribution of infected animals, and relative spore loads in soils.

PULMONARY COCCIDIOIDOMYCOSIS PRESENTING WITH INTERLOBULAR SEPTAL THICKENING

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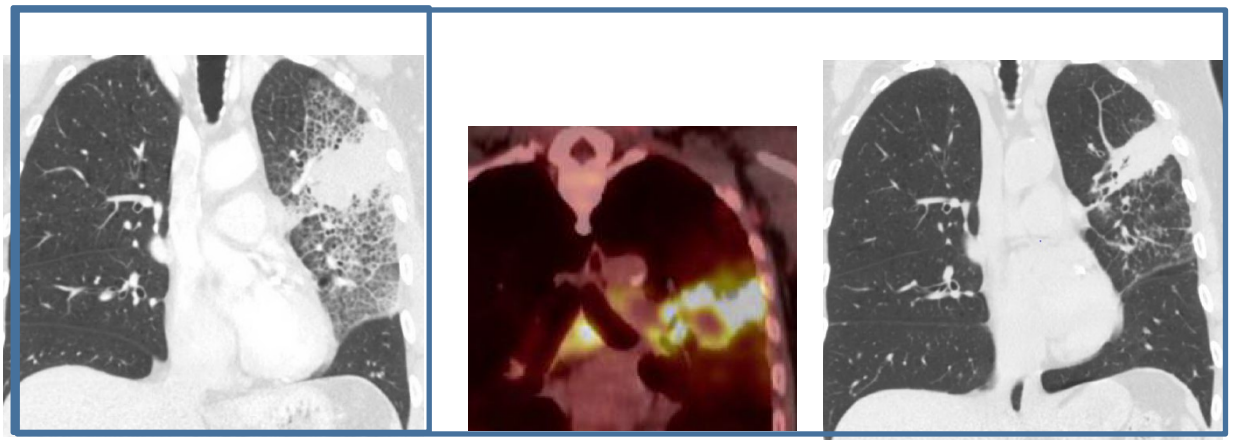
Introduction

Acute pulmonary coccidioidomycosis most commonly presents radiographically as consolidations (75%) or nodules (20%) and rarely as cavitation (2-8%), adenopathy (8%) or pleural effusions. Here, we present a unique case of acute pulmonary coccidioidomycosis presenting as intense septal thickening surrounding a large cavitary mass associated with mediastinal adenopathy. This "crazy paving" pattern has not yet been described in the literature to our knowledge for acute coccidioidomycosis.

Case Report

A previously healthy, 63-year-old male presented with 3 weeks of cough, low grade fever, weight loss and severe pleuritic chest pain. His chest imaging on admission revealed an 8 x 12 cm left upper lobe mass with surrounding extensive interlobular septal thickening. In addition, there were right lung nodules as well as bilateral hilar, subcarinal, left paratracheal and supraclavicular lymph node enlargement. (see Figure 1). The imaging was read as widespread lymphangitic carcinomatosis associated with primary lung cancer. The lung mass and lymph nodes were intensely hypermetabolic on PET-CT. A transthoracic biopsy was performed due to concern for malignancy and it showed necrotizing granuloma with spherules consistent with *Coccidioides* organisms. Blood tests revealed positive cocci IgM serology and complement fixation titer of 1:16. Sputum grew *Coccidioides immitis* as well. Patient was initially treated with antibiotics for presumed post-obstructive pneumonia for 7 days and then switched to fluconazole. Repeat imaging after 7 weeks of treatment showed complete resolution of the lymphangitic septal thickening and reduction in the size of the lung mass. Symptoms were still present but much improved from the time of presentation.

Figure 1. CT chest and PET-CT at presentation. **Figure 2.** CT chest at 7 weeks



Summary

This case describes an unusual cause of pulmonary coccidioidomycosis with extensive interlobular and intralobular septal thickening surrounding a cavitary mass. The extensive lymph node involvement suggests that this pattern might be due to lymphatic spread of the disease from the pulmonary source or due to disseminated disease. The presentation was highly suspicious for lung cancer, but the biopsy was key in making the early diagnosis.

SEVERE DISSEMINATED COCCIDIOIDOMYCOSIS IN A DOG WITH A MONOCLONAL GAMMOPATHY

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Introduction

A 4 YO SF mixed breed dog was referred for evaluation of progressive coccidioidomycosis failing voriconazole. Prior to referral, the dog had a three year history of coccidioidomycosis that had twice come out of remission, the first time within one month of stopping fluconazole, the second time within three months of a 30% reduction in the dose of itraconazole. The dog developed right hind limb lameness with effusion and a lytic lesion of the right tarsal joint. Aspiration cytology showed chronic inflammation with no etiologic agent identified. Protein electrophoresis triggered by globulins of 7.3 g/dl revealed a monoclonal gammopathy (5.5 g/dl). Coccidioidal antibody titer (ID) was 1:4 on a single test in the first year of treatment, but prior and subsequent tests were negative for anticoccidioidal antibody.

Methods

The dog's problem list at the time of referral included anorexia, progressive weight loss, bilateral pelvic limb lameness with difficulty ambulating, right hock swelling, tachypnea, dyspnea, intermittent fever, peripheral lymphadenopathy, and hyperglobulinemia (9.0 mg/dl). Thoracic radiographs revealed a miliary interstitial pneumonia. Aspiration and cytology of lymph nodes, spleen, and liver revealed abundant spherules in all sites, with no neoplastic cells seen. Amphotericin B infusions were instituted 3 times weekly, and oral voriconazole was continued with therapeutic drug monitoring. Anti-inflammatory prednisone (0.5 mg/kg/day) was instituted. The dog improved in attitude, appetite, and ambulation over the ensuing three weeks, then declined again with worsening lameness, depression and anorexia. Owners elected euthanasia, and the dog was necropsied.

Results

The dog had 2-10 mm greyish-tan lesions throughout the entire lungs in a reticulated pattern with edema and hemorrhage around the lesions. All thoracic and cranial mesenteric lymph nodes were grossly enlarged (1-6 cm). The right talocrural joint was filled with brown, flocculent fluid, and the distal tibia and talus were brown, grainy, and soft with destruction of bone. Histopathology revealed abundant spherules in lung, lymph nodes, bone marrow, distal tibia and hock joint, spleen, and liver. Sporadic spherules were seen in the kidney. Fixed lymph nodes were sent to Michigan State University for MUM-1, CD3 and CD79a staining. No evidence of multiple myeloma was seen. Lymph node lymphocytes appeared reduced, with effacement by spherules and granulomatous inflammation. Cultures of bone marrow (midshaft of right hind leg), joint fluid, lung, liver, spleen, and lymph nodes had heavy growth of Coccidioides spp. This strain had an in vitro MIC of 1 µg/ml to amphotericin B and 64 µg/ml to fluconazole in the University of Arizona Coccidioides laboratory.

Conclusion

This dog died of severe, disseminated coccidioidomycosis that failed treatment. The dog had very high globulins, and protein electrophoresis revealed a monoclonal spike. None of cytology, histopathology, or immunohistochemistry supported a diagnosis of multiple myeloma. Monoclonal gammopathies have been reported from dogs with severe pyoderma, leishmaniasis, and ehrlichiosis. It has not been previously reported in a dog with coccidioidomycosis. We suspect this patient had an underlying immune defect due to the long history of recurrent disease, but we lack the tools to identify it.

A CASE OF PRIMARY COCCIDIOIDOMYCOSIS COMPLICATED BY EMPYEMA

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Introduction Pulmonary coccidioidomycosis has been estimated to account for approximately 30% of community-acquired pneumonia in endemic areas in the American Southwest. Pleural effusion occurs in about 15% of hospitalized patients and is associated with fever, cough, and pleuritic chest pain. Empyema is an uncommon complication of primary pneumonia. Video-assisted thoracoscopic surgery (VATS) with decortication is an option for patients who fail tube thoracostomy drainage, but significant morbidity can occur as the result of prolonged air leaks due to bronchopleural fistula.

Case Findings A 37-year-old male with poorly-controlled type 2 diabetes presented with right-sided pleuritic chest pain for two weeks. He had previously completed a course of azithromycin without improvement. He reported night sweats and chills and was unable to take a deep breath due to pain. He was born in San Diego, California, employed as a social worker, had spent several years in Arizona for job training, and had never smoked. Initially, he was afebrile with a normal respiratory rate and an oxygen saturation of 93% on room air. He was in moderate distress taking shallow breaths and had rales in his right lung base. Initial laboratory studies revealed a mild leukocytosis with a negative influenza PCR. Chest radiography showed a large right lower lobe pleural effusion, and he was empirically started on vancomycin and piperacillin-tazobactam.

Clinical Course Over the next 24 hours, he rapidly decompensated with respiratory distress and hypoxemia. A CT scan demonstrated a loculated right pleural effusion with compressive atelectasis of the right lower and middle lobes. A pigtail chest tube was placed. *Coccidioides* serology was weakly positive and colonies of white mold were growing from sputum, raising concern for acute coccidioidomycosis. He was expectantly started on fluconazole. Pleural fluid was exudative with 54% polymorphonuclear cells and 40% lymphocytes. Sputum, pleural fluid, and serum ultimately grew *Coccidioides immitis*. Despite anti-fungal therapy and tube thoracostomy with twice daily tPA/DNAse administration, the patient's pain and pleural effusion persisted. He underwent VATS with lysis of adhesions, washout, and placement of a large-bore chest tube, however decortication was not performed due to the presence of friable, inflamed pleura. Fluconazole was switched to isavuconazole in the setting of prolonged QTc interval.

Outcome The patient gradually improved, was weaned off all oxygen support, and the chest tubes were removed. He was discharged with a prolonged course of antifungal therapy with a plan to consider decortication in the future.

Conclusion *Coccidioides* empyema is rare but should be suspected in the right clinical context. If tube thoracostomy fails to adequately drain the thorax, VATS with lysis of adhesions and washout should be considered. Severe pleural inflammation associated with pulmonary *Coccidioides* infections makes persistent bronchopleural fistula a common complication in patients requiring a surgical procedure. Delaying decortication in this setting may reduce morbidity. Future research is needed to compare outcomes of early versus late decortication in patients with coccidioidomycosis empyema.

PERITONEAL COCCIDIOIDOMYCOSIS PRESENTING AS A HERNIA

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Introduction

Very few individuals with coccidioidomycosis will develop extrapulmonary disease. If so, manifestations typically involve the skin, central nervous system, bones, or joints. Almost any site may be affected, but peritoneal coccidioidomycosis is considered rare. To this point, there is scant literature regarding the prognosis and treatment of this atypical dissemination. As with the majority of disseminated disease, the mechanism is presumptively hematomageous. To date, there is a paucity of reported cases of peritoneal coccidioidomycosis in the literature. We present a rare case of peritoneal coccidioidomycosis that presented in an asymptomatic patient as a hernia.

Methods

Retrospective chart review.

Results

We present the clinical course of a 46 year-old African-American male with no prior medical history who presented with umbilical and bilateral groin pain. Upon presentation, a CT scan demonstrated bilateral inguinal hernias as well as a small umbilical hernia defect. The patient then underwent a robotic-assisted laparoscopic bilateral inguinal hernia repair with primary peritoneal umbilical hernia. Upon entering the peritoneal cavity, there was noted to be diffuse peritoneal seeding with small white implants on the small bowel and the liver capsule. There was involvement of both the parietal and the visceral peritoneum. Additionally, small amount of omental caking was noted, raising concern for carcinomatosis peritonei or other infectious pathology. Given these intraoperative findings, the decision was made to abort the bilateral inguinal hernia repairs. Instead, peritoneal biopsies were taken and sent for frozen section and the umbilical hernia defect which measured 1 cm, was closed primarily. Tuberculosis (TB) quantiferon was negative and human immunodeficiency virus (HIV) antibody/antigen screen were found to be non-reactive. Thereafter, serum coccidioidal IgM was weakly positive, and serum IgG was positive by immunodiffusion test, with a complement fixation titer of 1:16. Subsequently, histopathology reports returned revealing granulomatous inflammation with endosporulating spherules consistent with coccidioidomycosis. Patient was then scheduled for follow-up in coccidioidomycosis clinic.

Conclusion

Coccidioidomycosis often has unusual clinical and radiographic presentations. This is one of a small number of cases in the literature that describes peritoneal coccidioidomycosis. The clinical presentation can range from indolent disease such as described above, or to an acute abdominal process with findings of peritoneal inflammation. The findings in the operating room were initially thought to be carcinomatosis. In endemic regions, coccidioidomycosis should be considered as a potential diagnosis as well as other infectious processes such as tuberculosis. This diagnosis can be made on the basis of granulomatous inflammation with demonstration of endosprorulating spherules on histopathology or can also be made on the basis of granulomatous inflammation with an appropriately performed coccidioidomycosis serology. It is our hope that this case will encourage further investigation and contribution of other reported instances of peritoneal coccidioidomycosis to highlight the unusual presentation of this important entity.

LOCUS MINORIS RESISTENTIAE IN COCCIDIOIDOMYCOSIS

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Introduction

Antecedent trauma is a known risk factor for hematogenous dissemination of infection; this also applies to coccidioidal species. We herein describe a patient who suffered from pulmonary coccidioidomycosis with subsequent trauma to the right tibia, resulting in osseous dissemination to the site of injury.

Method

This is a retrospective case report.

Case Report

43 year old man with a subacute cough and no other described symptoms suffered a right anterior tibial injury secondary to a fall from a forklift. At an urgent care there was no evidence of bony injury or a break in the integument; however, swelling, erythema and pain were appreciated at the site of injury.

Subsequent persistence of swelling, erythema and pain resulted in a visit to Kern Medical Emergency Department 30 days post initial trauma. Patient is noted to have cough and subjective fever, as well as pretibial swelling and erythema with no break in the epidermis. Imaging demonstrated right lower lobe pneumonic infiltrate and a lytic lesion in the right tibia. Operative management included saucerization and debridement. Cocci serology was negative for IgM and positive for IgG with a complement fixation titer of 1:32. Intraoperative cultures were positive for *coccidioides* species.

Conclusion

While *locus minoris resistentiae* is well described in bacterial infection, it is less appreciated in fungal infections including coccidioidomycosis. This is one of few cases of disseminated coccidioidomycosis associated with antecedent trauma. Although uncommon, clinicians should be aware of unexplained disseminated coccidioidomycosis secondary to trauma.

COCCIDIOIDOMYCOSIS CASES WITH PERSISTENTLY POSITIVE TEST RESULTS

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Introduction

Testing practices for coccidioidomycosis in the emergency department (ED) are not well understood. Some studies have suggested that coccidioidomycosis may be a common cause of community-acquired pneumonia (CAP) in Arizona and testing for coccidioidomycosis is uncommon in such patients. We describe characteristics of patients tested for coccidioidomycosis in EDs, trends in testing, and coccidioidomycosis testing among CAP patients in Arizona.

Methods

Testing provider and facility information, as well as ED visit records with admission dates between 1/1/2014 and 12/31/2016 were extracted from the Arizona hospital discharge database. Only records from adult Arizona residents with Current Procedural Terminology (CPT) codes for coccidioidomycosis testing were included. We also compiled a separate sample of patients with ED visits associated with CAP between 1/1/2014 and 12/31/2014. We defined CAP using ICD-9-CM discharge diagnosis codes for pneumonia due to infection. Exclusion criteria for this sample included patients who were not admitted from the community, were hospitalized in the 90 days prior to their ED visit, or were previously reported coccidioidomycosis cases. Only records with CPT codes for chest x-ray were included. Analyses were performed in SAS v9.4.

Results

In 2014, there were 2,672 ED visits with a CPT code for coccidioidomycosis testing. Excluding asthma with acute exacerbation (3.4%) and influenza (2.2%), the top 50% of principal discharge diagnoses reflected symptoms and syndromes consistent with primary pulmonary coccidioidomycosis. Sixty-one (10.3%) of 603 providers and five (8.9%) of 56 healthcare facilities accounted for half of all patients tested for coccidioidomycosis in the ED. Approximately one-third of all patients were tested at a single facility. There were 13,294 ED visits associated with CAP included in the analysis. The most common CAP-defining ICD-9-CM codes were pneumonia, organism unspecified (73.2%) and influenza (24.2%). Overall, 371 (2.8%) visits had a CPT code for coccidioidomycosis.

Conclusion

Our analysis demonstrated that coccidioidomycosis testing varied substantially by facility and provider. A small number of facilities and providers accounted for a disproportionate number of tested patients. More insight into clinical decision making regarding coccidioidomycosis testing in EDs is needed.

SEASONAL KERN COUNTY FARM WORKERS' KNOWLEDGE, ATTITUDES, BELIEFS AND BEHAVIORS REGARDING COCCIDIOIDOMYCOSIS (CDC/NIOSH 5U01OH010839)

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Introduction The coccidioidomycosis-related disease burden experienced by farm workers in highly endemic areas of California is not known. Mild cases are often undiagnosed, and severe disease may lead farm workers to return to Mexico, where cases are not reported. The contribution of empirical data from case reports is limited by missing occupational and ethnicity data. The Public Health goal is to ultimately understand and reduce farm worker exposure to coccidioidomycosis. This study provides data characterizing farm worker's knowledge and work practices previously lacking for designing, disseminating and evaluating primary and secondary prevention messages.

Methods Two migrant housing centers were accessed for resident interviews from June through October 2017 with the approval of the Kern County Housing Authority. Residents are required to have legal work permits and seasonal contracts with a local grower. Bilingual and bicultural male and female interviewers conducted interviews designed to assess demographics and outdoor agricultural history; coccidioidomycosis-related knowledge, attitudes, beliefs, behaviors and practices in the field; and experience with coccidioidomycosis, and sources of health information. Participant inclusion criteria were age $\geq$18 years, ability to provide informed consent and respond to questions in English or Spanish, and employment in outdoor farm labor in the previous 12 months. Participants were recruited from units randomly placed in sampling aliquots of 10 units. A new aliquot was selected from occupied units after up to 5 attempts were made to recruit 1 to 2 adult residents at each of the 10 units; this process was repeated until recruitment was completed.

Results Sixty-two males and 61 females (N=123) participated in the study. Ages ranged from 19 to 70 years, with a mean age of 42 years. 109 (88.6%) participants reported being born in Mexico. 34 (27.6%) participants had not previously heard of Valley Fever. 7 (5.7%) participants reported a diagnosis of Valley Fever; 52 (42.3%) reported having one or more friends, relatives or co-workers diagnosed with Valley Fever. Only 42 (34.1%) correctly responded that Valley Fever is not contagious. 78 (63.4%) correctly identified fever, cough and fatigue as Valley Fever symptoms. However, 46 (37.4%) agreed that *Coccidioides* spreads through contaminated food and water, 65 (55.3%) believed that it was acquired through pesticide use, and 71 (57.7%) reported concern about acquiring Valley Fever because they work with pesticides. 51 (41.5%) reported that wearing a bandana over the nose and mouth prevented Valley Fever; 61 (49.6%) stated that wearing a respirator prevented Valley Fever.

Conclusion Reports of Valley Fever diagnoses suggest risk in this population. Knowledge of Valley Fever was mixed. Bivariate associations of key knowledge and practice outcome variables and independent variables will be conducted to develop and test predictive models. Model results will be presented at the meeting, as well as a description of potential methods suggested by study results for modifying knowledge and risk behaviors.

Laboratory and Basic Science

Bridget Barker, Moderator

ANTI-COCCIDIOIDAL COMPLEMENT-FIXING TYPE (CF) ANTIBODIES RECOGNIZE FEW IF ANY CONTINUOUS EPITOPES OF THE CF ANTIGEN, CTS1.
Zong Y, Peng T, Johnson M, Lewis L, Frelinger J, Galgiani J

DEVELOPMENT OF A HIGH THROUGHPUT IMAGING FLOW CYTOMETRY (IFC) METHOD TO QUANTIFY FUNGAL CELLULAR STATES
Hung C, McMahon C, Esqueda M, Yu J

MEASURING THE NATURAL COURSE OF ANTIBODY PRODUCTION IN *COCCIDIOIDES* EXPOSED DOGS
Powell D^2, Hill K, Shubitz L, Trinh H, Butkiewicz C, Peng T, Bowen R, Bosco-Lauth A, Galgiani J, Frelinger J

DEVELOPMENT PATHWAY AND PROGRESS TOWARDS A USDA-APPROVED AVIRULENT LIVE VACCINE TO PREVENT COCCIDIOIDOMYCOSIS IN CANINES
Robb E, Hennessy K, Shubitz Lisa, Bowen R, Orbach M, Powell D, Frelinger J, Galgiani J

VALLEY FEVER COMPANION DIAGNOSTIC
Stafford P

ASSAYS TO OBTAIN vNAR FRAGMENTS FOR ENVIRONMENTAL *COCCIDIOIDES spp*.
Lopez-Tello J, Cabanillas-Bernal Ol, Licea-Navarro A, Riquelme M

HOST-PATHOGEN PROTEIN PROFILING OF COCCIDIOIDOMYCOSIS IN MULTIPLE HOST SPECIES
Mitchell N, Grys T , Lake D

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Break and **Posters Visitation**

ANTI-COCCIDIOIDAL COMPLEMENT-FIXING TYPE (CF) ANTIBODIES RECOGNIZE FEW IF ANY CONTINUOUS EPITOPES OF THE CF ANTIGEN, CTS1.

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Introduction

Detecting CF antibodies in the serum is highly specific for recent or active coccidioidomycosis and quantitative serial measurements have prognostic value. However, the CF antibody assay is technically complex and labor-intensive. At the last Annual Meeting of this group, we demonstrated that virtually all antibody-binding in human CF+ sera was restricted to the amino acid sequence from 111-310, less than half of the full-length CTS1 sequence. In this report, we study antibody binding to smaller CTS1 subunits.

Methods

CTS1 fragment 105-310 (more soluble than 111-310) and four overlapping peptides (#1=105-164, #2= 154-212, #3= 202-252, and #4= 240-310) were expressed in *Escherichia coli*. Because fragments #1, 3, and 4 were insoluble, solubility of these fragments was produced by expression of each with a maltose-binding protein (MBP) tag. All five expression products were analyzed on SDS PAGE and immunoblots with a human sera with CF=1:128. Enzyme-linked immune assays (EIA) were carried out with 96-well micro titer plates coated with recombinant peptides in excess, PBS, or MBP. Various dilutions of a human CF+ sera pool made from 50 sera (average titer= 12.6) or PBS were added and excess removed. Bound antibody was measured with an anti-human IgG second antibody conjugated with horse radish peroxidase and subsequent reaction with the chromophore, tetramethylbenzidine. Optical densities (OD) were read at 450 nm. Standard EIA curves were produced by coating wells with goat anti-human antibody or PBS and adding human immunoglobulin at concentrations from 2-14 ng/ml.

Results

$CTS1_{105\text{-}310}$ and the four overlapping fragments were all demonstrated to be expressed by SDS PAGE but CF antibodies only bound to $CTS1_{105\text{-}310}$. Similarly, EIA results with $CTS1_{105\text{-}310}$ demonstrated CF antibody binding at serum dilutions as great as 1:5,000 but <5% antibody binding was evident to any of the four overlapping fragments. Under the conditions employed, the reference standard curve was sensitive to 1 ng/ml of immunoglobulin.

Conclusion

$CTS1_{105\text{-}310}$ is the smallest antigenic peptide that is recognizable by anti-coccidioidal CF antibodies. The very minimal binding of CF antibodies to the four fragments overlapping $CTS1_{105\text{-}310}$ suggests that most if not all epitopes of $CTS1_{105\text{-}310}$ are discontinuous. Future directions include the use of EIA with $CTS1_{105\text{-}310}$ to be a quicker and more cost effective way of not only diagnosing coccidioidomycosis but also mimicking a quantitative CF titer in patient sera.

DEVELOPMENT OF A HIGH THROUGHPUT IMAGING FLOW CYTOMETRY (IFC) METHOD TO QUANTIFY FUNGAL CELLULAR STATES

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Introduction

High-performance and high-throughput automated image-processing techniques have been in increasing demand in the field of biology. The success of image-based profiling method hinges on assays that can rapidly and simultaneously capture a wide range of phenotypic features. We have developed an automated image acquisition and processing method using an imaging flow cytometer that can objectively measure over 500 characteristic features of a cell including size, shape, texture, nuclear DNA morphology, cell wall integrity and membrane permeability, etc. The method can be applied to characterize fungal mutants, screen antifungal compounds and measure cellular states upon exposure to drugs and environment factors.

Methods

We have first created reference sets of cytological profiles of Candida, Cryptococcus and Coccidioides after exposure to a set of clinical and experimental drugs against fungal cells. Control and treated fungi were stained with calcofluor white and FM4-64 FX that bind to fungal cell wall and lipophilic membrane for 30 min, respectively. Cells were processed in wells of a 96-well plate and images were acquired using an Amnies ImageStream MKII cytometer that could analyze up to 1000 cells per second. The image data were analyzed with IDEAS software using a batch processing with the same analysis template.

Results

We have run a pilot study to screen the Prestwick chemical library containing 1280 FDA-approved compounds for drugs that affected Cryptococcus cytological profile. Seventeen compounds were identified from the drug library and 12 drugs showed growth inhibition activity against Cryptococcus. Ten of these 12 compounds have been previously reported and/or patented to have antifungal activity. Two newly identified drugs can be potentially repurposed for antifungal treatment. This proof-of-concept study has confirmed that our IFC method is rapid, sensitive and reliable in quantification of fungal cellular states and identification of antifungals.

Conclusion

This image-based assay provides an unbiased approach to characterize compounds and cellular states to support future fungal biology study and antifungal drug discovery.

MEASURING THE NATURAL COURSE OF ANTIBODY PRODUCTION IN *COCCIDIOIDES* EXPOSED DOGS

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Introduction

Production of pathogen specific antibody can serve as a marker of both immune activation and pathogen exposure. Current methods of *Coccidioides* serology are based on either immunodiffusion or complement fixation. Here we develop a quantitative enzyme-linked immunosorbent assay (ELISA) to measure *Coccidioides* specific antibody production in both experimentally and naturally exposed dogs.

Methods

Purpose bred beagles were experimentally infected via nebulizer at a range of doses of *Coccidioides* and followed for clinical disease progression. Subjects were bled before exposure and at 2 week intervals following infection. Sera from the inoculated animals was used in a quantitative ELISA to measure specific antibodies to a small fragment (AA105-310) of the *Coccidioides* antigen Chitinase 1 (CTS1). Additionally, we tested serum from client owned dogs in the Tucson area that had no previous history of diagnosis or treatment for coccidioidomycosis and were being surveyed to identify subjects for cellular immunology studies. We also tested stored serum from clinically ill dogs that has been consented for prior studies.

Results

Experimentally infected animals showed increasing antigen specific IgG production following exposure. At the end of the experiment anti-CTS1 fragment antibodies reached a concentration of ~48 μg/ml. One particular animal showed no signs of disease after exposure and showed no IgG production, indicating that infection was never established. In client owned animals we have been able to detect *Coccidioides* antibodies in dogs that had no previous history of *Coccidioides* infection, inapparent infection. Retesting of known seropositive dogs from previous studies with the current EIA assay confirmed the commercial AGID serology results. Testing of 22 client dogs from North Carolina State University School of Veterinary Medicine, outside of the endemic area, showed no positive IgG.

Conclusion

Our quantitative ELISA is able to detect IgG production in dogs following both natural and experimental *Coccidioides* infection. Using experimentally infected animals allows us to observe the time course of antibody production and the rising antibody levels as the infection progresses. Lack of reactivity of the serum from dogs outside the endemic area suggests the test is specific for coccidioidal antibody.

DEVELOPMENT PATHWAY AND PROGRESS TOWARDS A USDA-APPROVED AVIRULENT LIVE VACCINE TO PREVENT COCCIDIOIDOMYCOSIS IN CANINES

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Introduction Deletion of the *cps1* gene from *Coccidioides posadasii* resulted in an avirulent mutant, Δ*cps1* that, as a vaccine in mice, produced exceptional protection against a subsequent lethal intranasal challenge with either the parent *C. posadasii* or *C. immitis*. The striking efficacy and apparent safety of *Δcps1* has led to NIH research support and a commercial licensee (Anivive Life Sciences) to undertake the development of a commercial canine vaccine. Success could drive continued development in man.

Methods To obtain a U.S. Veterinary Biological License a candidate vaccine must be made in an approved USDA Licensed Veterinary Biologics Establishment, based on an approved Outline of Production and derived from a qualified Master Seed that is tested to evaluate identity, safety and purity (freedom from exogenous agents). Summary Information Formats are required to provide additional safety and identity for all new live master seeds produced by DNA technology and to establish biocontainment and environmental safety. Protocols and reports for host animal immunology, effectiveness, safety, back passage, shed/spread, immunologic interference and other areas are negotiated and concurred with US Department of Agriculture, Animal and Plant Health Inspection Service, and Center for Veterinary Biologics (USDA APHIS CVB). Required supporting data include manufacturing process/procedures and validation reports, onset and duration of immunity studies in the target species, specifications and stability to assure whole vial potency at the end of shelf life based on validated potency assay. Finally, labels (claims) are reviewed and if approved by CVB a license is conferred.

Results Three components are necessary for the initiation of vaccine development: an antigen, a host species challenge model and a potency test. We have completed a study in six beagles titrating three escalating doses of aerosolized arthroconidia administered intratracheally to produce a coccidioidal infection over six to eight weeks. Preliminary analysis suggests a target infecting inoculum 10K to 100K arthroconidia. We have identified a licensed manufacturing facility (Hennessy Research Associates) and established a research project at Kansas University Center for Vaccine Stabilization to identify a final formulation. An ELISA for antibodies in canine sera is being developed as is a flow cytometry method to assess canine cellular response. Vaccine potency is assayed by direct spore counts and viability testing. Additional work is underway to support manufacture/scale up, and testing of canine effectiveness, target animal safety and safety in the environment.

Conclusion This program's goal is a Licensed Vaccine to prevent canine coccidioidomycosis. Goals for the coming year include further refining the canine challenge model, obtaining concurrence with CVB on the development plan, defining a stable formulation, completing process development/scale up and establishing the minimum immunizing dose and administration frequency.

VALLEY FEVER COMPANION DIAGNOSTIC

Phillip Stafford

Biodesign Institute, Tempe, AZ

Introduction

Valley Fever diagnosis has a reputation for evading current serological tests for antibody reactivity to coccidiodes proteins. Many patients report multiple visits to the clinic before they are diagnosed sero-positive. Conversely, most AZ residents, especially those in the Phoenix/Tucson I-10 corridor become sero-positive at a conversion rate of approximately 10%/year. There is a need for a highly sensitive Valley Fever diagnosis with low false positives. Immunosignatures represent a new type of serological test that uses hundreds of thousands of random-sequence peptides to diagnose disease using a single drop of blood. The signature of an infected person can be distinguished from endemic Arizona residents, and we find that our diagnosis is earlier and more sensitive that the existing diagnosis. This puts immunosignatures into a unique position to be used as a companion diagnostic for clinical trials.

Methods

Immunosignatures are composed of a dense microarray of 125,000 unique peptides that bind to IgG from infected patients. Immunosignatures must be trained to recognize the Valley Fever signature. Once trained, we test the performance on blinded samples. We recently obtained serum samples from three volunteers who complained of VF-like symptoms, and a long-term unresolved cough. We also have blood from hundreds of medium-titer confirmed posadasii patients from Sonora Quest laboratories (Phoenix, AZ) to use as training samples.

Results

We processed 50 serum samples from persons identified as posadasii-infected and 50 samples from persons infected with immitis. We identified a species-specific signature, we identified a local AZ-based non-infected endemic exposure signature, and we identified an ‘early’ VF signature.

Conclusion

We believe the key to successful drug development is a sensitive and specific diagnostic for detecting Valley Fever. We found three unique signatures of Valley Fever – a strong infection signature from people who were diagnosed with disease using the standard serological VF test. This signature could discriminate posadasii from immitis. We also could distinguish long-term Phoenix residents from non-residents using only VF signatures. Lastly, we believe we can discriminate between early VF and late VF. Early VF is difficult to distinguish. Turning up the sensitivity too high on standard diagnostics increases false positives. We do not see false positives at the level where we can see low-grade VF signatures. This is an important distinction when testing VF drugs.

ASSAYS TO OBTAIN vNAR FRAGMENTS FOR ENVIRONMENTAL *COCCIDIOIDES spp.*

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Introduction

Given the high cost, low sensitivity, and special requirement needs of the currently available tests for *Coccidioides* spp., the goal of this project is to design a new detection method using single domain antibodies that would permit an opportune environmental detection of risk zones, at the same time reducing the risk of exposure of researchers to the etiological agent. This outcome would facilitate better epidemiologic studies in the future.

Methods

The antibody selection was performed by vNAR fragment panning through non-immune phagemid libraries. Libraries construction consist of a pComb3x phagemid vector that contain an IPTG promoter, a HA-tag, a 6xHis sequence, an amber codon, and a variant coding sequence of vNAR fragments in conjunction with helper phage for phage assembly. Biopanning experiments were done using coccidioidin and IDTP IMMY© antigen. Input and output titrations were performed by *E. coli* infection using the isolated phagemids in each round. Resulting clones were analyzed by ELISA to verify if the antibody fragments were expressed in complete phagemids. Clones were grown in liquid cultures, processed for alkaline plasmid extraction and sequenced to verify a correct open reading frame. We obtained soluble vNAR proteins through *E. coli* transformation and protein overexpression in liquid cultures. Proteins were extracted from bacterial periplasm by osmotic shock; extracts were analyzed by ELISA for protein expression and antigen recognition, and the extracted proteins purified by affinity chromatography.

Results

After the biopanning, 22 phagemids were processed for sequencing. The sequences were analyzed for common antibody fragment domains and correct ORF, and seven different clones were selected for protein expression. After extracts were analyzed for protein expression and antigen recognition, five clones were found capable of recognizing the antigens and were further purified for protein-antigen recognition assays.

Conclusion

Although the extracts showed a high level of recognition for *Coccidioides* antigens, it is necessary to determine the purified proteins-antigens affinity. Once this is proven, it will be important to study the interaction between the protein and soil samples as well as pure *Coccidioides* cultures.

HOST-PATHOGEN PROTEIN PROFILING OF COCCIDIOIDOMYCOSIS IN MULTIPLE HOST SPECIES

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Introduction This study provides a proteomic snapshot of host and fungal *Coccidioides spp.* proteins during lung infection in 3 host species; mouse, human and dog, to better understand the potential interplay between host and fungal pathogen. Also provided is a proteomic comparison of the immune response of Balb/c mice infected with either *C. posadasii* strain Silveira, or a Δ*cps1* mutant currently being explored as a vaccine candidate.
Methods Mass spectrometry analysis was performed on Coccidioides-infected and control lung tissue samples from human (n=4 diseased, 3 control), mouse (n=3, 3), and dog (n=1, 1) in triplicate technical runs. A naturally infected dog lung and three lab-infected Balb/c mouse lung samples were kindly provided by Lisa Shubitz of University of Arizona; 1 infected with *C. posadasii* strain Silveira (WT, ATCC 28868) and 2 mice with high-dose *C. posadasii* Δ*cps1* mutants generated by Marc Orbach. Spherules and immediately surrounding host tissues from FFPE lung tissue sections were extracted using laser capture microdissection. Proteins were in-solution digested prior to nano-LC MS/MS. Statistical analyses were performed in Scaffold v.4.8.4 (Proteome Software Inc.), using a 2% FDR.
Results *Host proteins:* In mice, 1237 total host proteins were identified; 368 significantly more abundant in infected mice and 185 significantly less abundant, relative to healthy mouse lungs. In humans, 1285 total host proteins were identified; 60 significantly increased and 50 significantly decreased in abundance during infection. In dogs, 904 total host proteins were identified; 68 significantly increased and 37 significantly decreased during infection. ECM associated proteins, laminin and collagen were both significantly less abundant in all host species during infection. *Coccidioidal proteins:* A total of 1030 Coccidioidal proteins were identified from all 3 host species combined; 567 from human, 1025 from mice, and 280 from dog. Only 3 unique Coccidioidal proteins were found in human lung infections and 2 unique in dog lungs. There were 421 unique Coccidioidal proteins in mouse lungs which could be due to i) the permissive strain of mouse (Balb/c) used and ii) the large experimental inoculum of arthroconidia. *Δcps1 vs. WT Silveira infected mice:* Only 2 Coccidioidal proteins were significantly different between the Δ*cps1* and WT Silveira strain in Balb/c mice, whereas the host response had 21 proteins of increased abundance; 3 were interferon-gamma inducible factors previously shown to be associated with the natural resistance of DBA/2 mice to *Coccidioides spp.* infection; 1 MHC class I protein and an aspartyl protease, both previously associated with CD8+ T cell-mediated cytotoxicity and protective immunity in mice. 60 proteins were significantly more abundant in response to the WT Silveira strain, 16.7% (n=10) of which were antibody fragments associated with a non-protective Th2 response.
Conclusion This study is the first comprehensive evaluation of the *in vivo* proteome of both host and pathogen in *Coccidioides spp.* infections in 3 different mammalian hosts. In the limited samples tested, *in vivo* Coccidioidal protein abundance was similar in all host species. However, significant differences in host protein abundance was observed, suggesting caution should be taken when extrapolating findings about immune responses from mouse models. Also provided is evidence that the *Δcps1* vaccine strain significantly alters the host proteins towards a protective Th1 response rather than altering expression of Coccidioidal proteins in mice.

Epidemiology-Ecology

Rebecca Sunenshine, Moderator

REVIEW OF COCCIDIOIDOMYCOSIS ENDEMIC PARAMETERS IN MÉXICO
Castañón-Olivares L, Muñiz-Salazar R, Candolfi O, Lezama A

THE EFFECTS OF CLIMATE CHANGE ON COCCIDIOIDOMYCOSIS ENDEMIC REGIONS IN THE UNITED STATES
Gorris M, Treseder K, Zender C, Randerson J

COCCIDIOIDOMYCOSIS IN THE SURROUNDING LAND MASSES OF THE CARIBBEAN SEA IS CAUSED BY CRYPTIC *COCCIDIOIDES POSADASII* POPULATIONS
Teixeira M, Matute D, Alvarado P, Hepp C, Roe C, Sahl J, Thompson G III, Arathoon E, Galgiani J, Engethaler D, Barker B

INCREASE IN REPORTED COCCIDIOIDOMYCOSIS CASES IN ARIZONA FROM OCTOBER, 2017 THROUGH JANUARY, 2018
Bezold C, Khan M, Brady S, Adame G, Sunenshine R, Komatsu K

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REVIEW OF COCCIDIOIDOMYCOSIS ENDEMIC PARAMETERS IN MÉXICO

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Introduction In 1958 Fiese published: A region is considered endemic to coccidioidomycosis if it meets the following four requirements:

- Reports of clinical cases.
- Positive reaction to coccidioidin in humans and pets.
- Presentation of cases in domestic and wild animals.
- Fungal isolate from soil.

Baja California, Sonora, Chihuahua, Coahuila, Nuevo León and Tamaulipas are states in northern Mexico that have been considered endemic to *Coccidiodes spp*. infection; however, it is unknown which of them complies with those features indicated by Fiese. The objective of this work was to identify, at present, the Mexican states that comply with coccidioidomycosis endemicity requirements.

Methods The epidemiological indexes of morbidity and mortality in humans, published by the Ministry of Health, were investigated through the electronic databases. The presence of coccidioidomycosis in wild animals, have been carried out through serological tests in search of anti-*Coccidioides* antibodies. The prevalence of infection was investigated with skin test/coccidioidin surveys, in humans and domestic animals, and finally cultures of soils *in vitro* was performed for to know the presence of *Coccidioides spp*. in this substrate.

Results Through studies conducted in Mexico since 2000, it has been found that: In the period 2000-2014, there is a report of 561coccidioidomycosis human cases in our country from which 49 were diagnosed in Baja California, 293 in Sonora, 19 in Chihuahua, 6 in Coahuila, 5 in Nuevo León and 5 in Tamaulipas. During 2010-2011, a survey with coccidioidin was performed on 1,081 people and the percentage of positivity of the test was 37.5% in Baja California, 67.0% in Sonora, 49.5% in Coahuila and 39.8% in Nuevo León. In Baja California, the skin test with coccidioidin was applied in 50 domestic dogs, of which only 2 were positive. The presence of anti-*Coccidioides* antibodies in domestic dogs has been carried out in Baja California and Coahuila and in wild animals in Baja California and Chihuahua. Finally, the isolation of *Coccidioides spp.* from soil has only been reported in Baja California.

Conclusion At the moment, only the Baja California state meets the parameters of Fiese. However, the definition of endemic does not take into account:

- The sites of diagnosis of the disease are not always the places where the patient became infected.
- The capture of wild animals must be carried out by an expert, a situation that makes it difficult to verify that wild animals suffer coccidioidomycosis.
- The immunological response in domestic dogs is different from that of humans, so skin tests are not suitable to check previous infection in pets.
- The great difficulty of the isolation of the fungus from the soil allowed to develop molecular methods for the identification of DNA of *Coccidioides spp*. what seems to be more promising

Therefore, the experience suggests updating the concept of endemic area for coccidioidomycosis.

THE EFFECTS OF CLIMATE CHANGE ON COCCIDIOIDOMYCOSIS ENDEMIC REGIONS IN THE UNITED STATES

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Introduction

Previous studies show temperature and precipitation are two main climate drivers that influence coccidioidomycosis dynamics (e.g., Gorris et al., 2018). Climate projections for the western United States indicate temperatures will increase and precipitation patterns may shift. These changes may influence what areas are endemic for coccidioidomycosis and how many people contract this disease. Our study examined how climate change may influence the spatial structure and magnitude of coccidioidomycosis incidence. We estimated current and future areas endemic for coccidioidomycosis and modeled mean annual incidence for years 2025, 2055, and 2085. Our model may guide public health agencies to implement disease surveillance programs and improve health outcomes, especially for vulnerable populations.

Methods

We used a southwestern US regional coccidioidomycosis database we previously compiled to quantify the relationships between coccidioidomycosis incidence and mean annual temperature and mean annual precipitation. We used future climate projections from downscaled Earth system models created by AdaptWest for years 2025, 2055, and 2085, examining both a moderate and large global warming scenario. We defined counties as endemic for valley fever if they met our mean annual temperature and mean annual precipitation threshold values. We determined these threshold values by maximizing the accuracy of our 2000-2015 county-level endemicity map against the U.S. Centers for Disease Control and Prevention (CDC) endemicity map as true. We then estimated future coccidioidomycosis mean annual incidence using a nonlinear model relating 2000-2015 incidence and mean annual climate conditions.

Results

Our model estimated that currently 12 states are possibly endemic for valley fever, which is greater than the CDC estimate of 7 states. By 2085, our model estimated 16 states will be endemic under a moderate warming scenario and up to 18 under a large warming scenario. By 2085, the number of cases may increase up to 35% under moderate warming or 80% under large warming. Warmer temperatures in the US may expand coccidioidomycosis endemic regions northward, while precipitation patterns will ultimately control which counties on the western half of the US are endemic. Drier counties within mountain rain shadows are likely to be endemic, whereas counties along the western coast that continue to receive ample rainfall will not be endemic.

Conclusion

As temperatures increase and precipitation patterns change, a greater extent of the US, and a large portion of the western US, will have climate conditions suitable for coccidioidomycosis endemicity.

COCCIDIOIDOMYCOSIS IN THE SURROUNDING LAND MASSES OF THE CARIBBEAN SEA IS CAUSED BY CRYPTIC *COCCIDIOIDES POSADASII* POPULATIONS

Teixeira MM[a,b], Matute DR[c], Alvarado P [d], Crystal M. Hepp[b], Roe C[b], Sahl J[b], Thompson III GR[e], Arathoon E[f], Galgiani J[g], Engethaler D[a], Bridget M. Barker[a,b]

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Introduction *Coccidioides posadasii* is a pathogenic fungus that causes coccidioidomycosis in the southwestern United States, Central and South Americas. Our previous work indicates that *C. posadasii* is comprised of at least three populations; ARIZONA, TEXAS/MEXICO/SOUTH_AMERICA (TX/MX/SA) and GUATEMALA. The exact range of *C. posadasii* and its role on human and animal infections in Central and South America is undetermined: the disease in these countries is sub-notified to local health departments, and fewer than 1,000 total coccidioidomycosis cases across the region have been reported. The Caribbean region is bordered by the Caribbean Sea, and its surrounding continental landscapes and islands may play an important role in the dispersion of *C. posadasii* across South America through Southeastern Mexico, Honduras, Guatemala and Venezuela.

Methods To better define the genetic distribution and population dynamics of *C. posadasii* in Central and South America, we *de novo* sequenced the genomes of 6 *Coccidioides* sp. clinical isolates from Venezuela, 2 from Mexico as well 1 from Texas and 1 from Florida (USA). We performed phylogenomic and population genomics analysis by incorporating 52 previous deposited genomes from *C. posadasii* (TX/MX/SA), ARIZONA and GUATEMALA populations to identify the genetic background of Venezuelan strains and better understand dispersion of this species complex into Central and South America.

Results Comparative phylogenomic analyses of *C. posadasii* complex reveal that clinical strains from Guatemala and Venezuela are reciprocally genetically isolated from the well described populations ARIZONA and TX/MX/SA. Population genomics data indicates that limited gene flow exists between GUATEMALA and ARIZONA populations, whereas complete reproductive isolation from all *C. posadasii* lineages was observed in the VENEZUELA population. Based on these observations, new patterns of dispersion through Central and South America of this pathogen complex is proposed.

Conclusion By using comparative genomics and population genetics tools we provide strong evidence that the South American continent was colonized by at least two ancestral populations: TX/MX/SA and VENEZUELA. ancestral genotype, and the second by a GUATEMALA ancestral genotype. The isolates from Brazil and Paraguay cluster within the TX/MX/SA cluster whereas the Venezuelan clade shares a common ancestor with the Guatemalan cluster and together forms the "Caribbean clade." Thus, the data suggest that the Venezuela lineage was purified through migration through Central America to the semi-arid regions of Venezuela, especially in the coastal plains of the Paraguaná peninsula and the depression valleys of Lara and Falcon states.

INCREASE IN REPORTED COCCIDIOIDOMYCOSIS CASES IN ARIZONA FROM OCTOBER, 2017 THROUGH MARCH, 2018

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Introduction

Arizona is experiencing a substantial increase in reported cases of coccidioidomycosis. New coccidioidomycosis cases reported monthly to the Arizona Department of Health Services (ADHS) during October 2017– March 2018 exceeded same-month averages during 2013–2016 by 18%–100%. We described demographic and laboratory characteristics of reported cases for the current increase and compared them to cases reported in the same months one year prior.

Methods

Coccidioidomycosis cases were identified through the state's Medical Electronic Disease Surveillance Intelligence System (MEDSIS); demographic characteristics (age, gender, and county of residence) and laboratory results were extracted. The collection date of the first positive laboratory test was used as the index date. To account for the seasonal pattern of coccidioidomycosis, we compared demographic and laboratory characteristics of cases reported during October 2017–March 2018 with cases reported during October 2016–March 2017. Laboratory test results were classified using a SAS-based string matching algorithm. *P*-values were calculated using chi-square tests for categorical variables and t-tests for continuous variables.

Results

Coccidioidomycosis cases were identified through the state's Medical Electronic Disease Surveillance Intelligence System (MEDSIS); demographic characteristics (age, gender, and county of residence) and laboratory results were extracted. The collection date of the first positive laboratory test was used as the index date. To account for the seasonal pattern of coccidioidomycosis, we compared demographic and laboratory characteristics of cases reported during October 2017–March 2018 with cases reported during October 2016–March 2017. Laboratory test results were classified using a SAS-based string matching algorithm. *P*-values were calculated using chi-square tests for categorical variables and t-tests for continuous variables.

Conclusion

Monthly reported coccidioidomycosis case totals in Arizona in late 2017 and early 2018 are among the highest in recent years. While the volume of cases is elevated, the age and sex distributions and laboratory profiles of the current increase are similar to patterns observed in previous years. The increase in cases is unlikely to be a laboratory artifact; additional work is needed to understand the factors that may be driving the observed increase. Sharing information with providers and the public about the increase in coccidioidomycosis can help ensure early detection and appropriate treatment.

Clinical Science

Susan Hoover, Moderator

***THE UTILITY OF SCREENING FOR COCCIDIOIDOMYCOSIS IN RECIPIENTS OF ANTI-TUMOR NECROSIS FACTOR ALPHA THERAPY**
Blair J, Choi K, Deval N, Vyas A (CSG-7)

***THE VALUE OF ROUTINE SEROLOGICAL SCREENING FOR COCCIDIOIDOMYCOSIS IN PATIENTS ON ANTIRHEUMATIC THERAPY**
Bilal J, Sudano D, Kollampare S, Bode B, Lisse J, Hoover S, Ampel N (CSG-35)

***Roundtable Discussion of Immune Suppression and Coccidioidomycosis by J Bilal and J Blair**

COCCIDIOIDOMYCOSIS COMPLEMENT FIXATION TITER TRENDS IN THE AGE OF ANTIFUNGALS
McHardy I, Dinh B, Thompson G III (CSG-12)

A RETROSPECTIVE REVIEW OF CANINE COCCIDIOIDOMYCOSIS CASES AT A TERTIARY CARE CENTER IN TUCSON
Butkiewicz C, Shubitz L (CSG-10)

POSACONAZOLE AND ITRACONAZOLE INDUCED HYPERTENSION AND HYPOKALEMIA: MECHANISM AND TREATMENBT IMPLICATIONS
Thompson D III, McHardy I, Chang D, Wittenberg R, Semrad A, Hoffman W (CSG-4)

****DELAYS IN DIAGNOSIS OF COCCIDIOIDOMYCOSIS IN TUCSON, ARIZONA**
Donovan, F, Wightman P, Majeed A, Gabe Luke, Zong Y, Galgiani J (CSG-8)

****RAPIDITY OF COCCIDIOIDOMYCOSIS DIAGNOSIS AND ITS EFFECT ON HEALTHCARE UTILIZATION**
Ginn, R[1], Mohty, R, Bollmann, K, Galgiani, J, Mendez, G, Goodsell, J (CSG-38)

****ANTIBIOTIC AND ANTIFUNGAL TREATMENT AMONG PATIENTS WITH COCCIDIOIDOMYCOSIS IN SOUTHERN CALIFORNIA 2011**
Chi G, Benedict K, Beer K, Jackson B, McCotter O, Xie F, Lawrence J, Tartof S (CSG-26)

****Roundtable Discussion of Strategies to Avoid Diagnostic Delay**

THE UTILITY OF SCREENING FOR COCCIDIOIDOMYCOSIS IN RECIPIENTS OF ANTI-TUMOR NECROSIS FACTOR ALPHA THERAPY

Blair, JE, Choi, K, Deval, N, Vyas, A.
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Introduction
Tumor necrosis factor-α inhibitors (TNF-I) are commonly used to treat a wide variety of immune-mediated disorders. These medications are linked to an increased risk of mycobacterial, viral, and fungal infections, and some society guidelines recommend screening for tuberculosis, hepatitis B and C, and human immunodeficiency virus prior to initiating
TNF-I therapy. Patients are also commonly screened for coccidioidomycosis in Arizona, but there is as yet no evidence on which to base this practice. The aim of this study was to compare outcomes of cohorts of selected TNF-I recipients who were screened for coccidioidomycosis with those who were not so screened, to determine the number of patients presenting with symptomatic coccidioidomycosis in each group, and to describe outcomes of patients with abnormal coccidioidal screening.

Methods
We electronically searched for all patients at our institution receiving TNF-I from 9/4/2010 to 9/26/2016, and included patients who were prescribed TNFI for dermatologic, rheumatologic, or gastroenterological purposes. We then categorized patients by whether or not they had undergone any serological testing for coccidioidomycosis, whether such testing was for screening or diagnostic purposes, and whether or not such studies were positive.

Results
From 9/4/2010 through 9/26/2016, 2793 patients had a TNF-I prescribed, of whom 1951 met inclusion criteria for study; Among the 1951, 1025 (52.3%) had never had any screening serology performed, and 926 (47.5%) had coccidioidal serologies performed either prior to initiation of TNF-I (baseline screen) and/or at an established time thereafter (annual screen). Among the 1025 TNF-I recipients without any coccidioidal screening, 35 (3.4%) developed symptomatic coccidioidomycosis. Among the 926 patients who had undergone screening for coccidioidomycosis, 53 (5.7%) were identified as having an abnormal screen (7 probable infection, 11 possible infection, 18 asymptomatic seropositive, and 17 EIA IgM only). Twelve of 926 (1.3%) developed symptomatic coccidioidomycosis after the screen. When compared with the screened cohort, the unscreened cohort was significantly more likely to develop symptomatic coccidioidomycosis (35/1025 versus 12/926, p=.003) Of the 53 patients whose abnormal coccidioidal screens were identified, 34/53 (64.2%) were identified on baseline screening, and 19/53 (35.8%) were identified on subsequent annual screens.

Conclusion
Within the *Coccidioides*-endemic area, screening for asymptomatic coccidioidomycosis allowed the identification and management of coccidioidomycosis prior to initiation of TNF-I in 5.7% of patients. There was significantly less symptomatic coccidioidomycosis among the screened than unscreened cohort. These results provide guidance in the approach to patients starting TNF-I in *Coccidioides*-endemic regions.

THE VALUE OF ROUTINE SEROLOGICAL SCREENING FOR COCCIDIOIDOMYCOSIS IN PATIENTS ON ANTIRHEUMATIC THERAPY

Bilal J, Sudano D, Kollampare S, Bode B, Lisse J, Hoover S, Ampel NM.

The University of Arizona Arthritis Center and the Southern Arizona Veterans Affairs Health Care System (SAVAHCS), Tucson, AZ.

Background

Coccidioidomycosis is an endemic fungal infection in the southwestern United States that may cause life threatening disease, particularly among patients on immunosuppressive therapy. Because of this, some clinics periodically screen for coccidioidomycosis in rheumatology patients on immunosuppressive therapy using coccidioidal serology. However, the value of this is unproven.

Methods

We conducted a retrospective study between 2007 and 2015 at two arthritis centers in Tucson, AZ and identified patients who were on disease-modifying antirheumatic drugs (DMARD) or biological response modifying (BRM) therapy who were found to have a positive coccidioidal serology during routine yearly screening. Serological screening including IgM and IgG performed by enzyme immunoassay (EIA), and immunodiffusion (IDTP and IDCF).

Results

Nineteen patients were identified with positive coccidioidal serology who were asymptomatic. Among these, 13 continued antirheumatic therapy without interruption. Of the six patients who had an interruption; three were restarted within one month. Thirteen of the 19 patients received no antifungal therapy, including 10 who remained on antirheumatic therapy. The other six were started on fluconazole, ranging from 8 to 73 months (median 30.5 months). After a median follow-up of 43 months, no patient developed clinically active coccidioidomycosis.

Overall, 13 had only a positive EIA serological test, including seven with a positive IgM EIA alone; four with a positive IgG EIA alone; and two with both IgM and IgG EIA positive. The other four had positive immunodiffusion tests and two had complement fixation positive.

Conclusion

These results suggest that continued anti-rheumatic therapy is safe in asymptomatic patients with positive coccidioidal serological tests and also suggest that routine implementation of antifungal therapy may not be warranted in this group of patients. Finally, the findings raise concern regarding the utility of routine serological screening of asymptomatic patients residing in the coccidioidal edemic area, and particularly raise concerns about using EIA

COCCIDIOIDOMYCOSIS COMPLEMENT FIXATION TITER TRENDS IN THE AGE OF ANTIFUNGALS

Ian McHardy[1], Bao-Tran Nguyen Dinh[1], George R. Thompson III[1,2]

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[2] Department of Internal Medicine, Division of Infectious Diseases, University of California Davis Medical Center, Sacramento, CA; USA

Background
Coccidioidomycosis is associated with a broad spectrum of illness severity, ranging from asymptomatic or self-limited pulmonary infection to life-threatening manifestations of disseminated disease. Serologic studies by Smith *et al.* from the early 1900s, before the widespread availability of antifungals, indicated that disseminated coccidioidal infections were most often associated with coccidioidal complement fixation antibody titers greater than 1:16. Since then, effective antifungal therapy has become available and altered the natural history of disease. The effects of antifungal therapy on serologic characteristics has not previously been evaluated.

Methods
To revisit and expand upon clinical correlates of coccidioidal complement fixation titers in the era of antifungal therapy, we retrospectively analyzed chart history and titer trends of 434 patients classified by infectious disease physicians as having either uncomplicated pulmonary coccidioidomycosis (UPC) (n=248), chronic pulmonary coccidioidomycosis (CPC) (n=64), disseminated coccidioidomycosis not including meningitis (DC) (n=86), or coccidioidal meningitis (CM) (n=36) – all patients in this cohort received antifungal therapy. Maximal complement fixation titers, time to maximum titer, titer reduction rate from maximum titer, and number of serologic 'recurrences,' defined as ≥2 dilution increase in titer after at least 90 days from initially positive serology, were calculated for each patient and results were compared for each group.

Results
Roughly 17% of UPC, 50% of CPC, 80% of DC, and 58% of CM patients developed maximum complement fixation titers greater than 1:16. Surprisingly, 25.4% of UPC, 6.3% of CPC, 2.3% of DC, and 8.3% of CM patients did not develop a detectable complement fixation titer during the study period (at least 3 years after diagnosis for each patient). The median maximum titer was 1:4 (range <1:2 – 1:512) for UPC, 1:32 (range <1:2 – 1:2048) for CPC, 1:128 (range <1:2 – 1:4096) for DC, and 1:32 (range <1:2 – 1:4096) for CM patients. Maximum titer developed a median 18 days after initial positive serology for UPC, 67.5 days for CPC, 52 days for DC, and 72 days for CM. Serologic recurrences occurred on average 0.14 times per patient for UPC, 0.55 times per patient for CPC, 0.94 times per patient for DC, and 0.88 times per patient for CM. Median days for a one dilution reduction in titer was 84 for UPC, 112 for CPC, 156 for DC, and 155 for CM.

Conclusion
Our findings provide an update on prior serologic studies performed prior to long-term triazole therapy. An understanding of the serologic kinetics for patients with varying forms of coccidioidomycosis receiving antifungal therapy is key to clinical evaluation and therapeutic decision making.

A RETROSPECTIVE REVIEW OF CANINE COCCIDIOIDOMYCOSIS CASES AT A TERTIARY CARE CENTER IN TUCSON

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Introduction

Previous studies have assessed the clinical signs and diagnosis of coccidioidomycosis in dogs. However, few studies have attempted to evaluate these patients through a follow up period. This study retrospectively reviewed the medical records of dogs in Tucson, AZ to determine the relationship between the quantitative immunodiffusion (ID) titer and disease severity both at diagnosis and at least one year later.

Methods

Possible cases were identified through a database search of patients seen at the Veterinary Specialty Center of Tucson (VSCOT) between 2011 and 2015. Paper and computer records were reviewed to identify cases appropriate for this study. Cases included had to have records tracing back to the initial diagnosis and at least one year of follow up care. Severity of disease was scored by using a modification of the scoring system developed by the Mycosis Study Group, in which one point was assigned to clinical signs of disease and laboratory abnormalities and two points were assigned to radiographic abnormalities.

Results

Ninety-nine dogs with complete information in their records were included in this retrospective study. At diagnosis, 88/99 dogs had primary pulmonary disease, while 11 dogs had dissemination to the bone (6), skin (2), nervous system (2), or joints (1). Quantitative ID titers at diagnosis ranged from negative (n=16) to ≥1:256. Disease score at diagnosis ranged from 0 to 10 (mean=5.23). There was no significant correlation between the disease score and the ID titer at diagnosis. During the follow up period, an additional 21 dogs developed disseminated illness, with the most common site of dissemination being bone. Eighty-four dogs had exams and diagnostic test results that could be associated with an ID titer after at least 1 year of follow up. At that time point, ID results ranged from negative (n=5) to ≥1:256. Disease score in these dogs ranged from 0 to 9 (mean=0.9). Moderate positive correlation ($r=0.4325$, $p<0.0001$) between disease severity and ID titer was evident at the follow up time point. Fluconazole was overwhelmingly the first line treatment chosen. Twenty-seven of the dogs failed the initial therapy and were switched to a different antifungal drug. Ten dogs developed recurrent disease between 4 months and 5 years after discontinuation of initial therapy (mean=1.8 years). Five of these dogs progressed from primary to disseminated illness at the time of recurrence.

Conclusion

Our review of records from dogs in a tertiary care setting suggests that there is little correlation between disease severity and a quantitative ID titer. Quantitative ID titers should be interpreted in conjunction with the entire clinical picture of the patient. Disease recurrence occurred in about 10% of our population. Recurrence occurred even years after initial diagnosis, and disease often became more severe.

POSACONAZOLE AND ITRACONAZOLE INDUCED HYPERTENSION AND HYPOKALEMIA: MECHANISM AND TREATMENT IMPLICATIONS

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Background
Posaconazole and itraconazole are frequently used in the treatment of refractory or disseminated coccidioidomycosis. Higher serum itraconazole and posaconazole concentrations have been associated with improved clinical responses for other fungal infections, and higher doses are increasingly used by infectious diseases providers. However, higher serum and tissue levels are likely to reveal previously undescribed toxicity as adverse events attributed to "off-target" effects are observed.

Methods
We prospectively identified three patients with new onset hypertension, hypokalemia and alkalosis after starting itraconazole or posaconazole tablets. Patient vital signs and laboratory values were within normal limits prior to starting these triazoles. However, following over 30 days of therapy all patients became newly hypertensive (mean systolic BP increase 59 mm Hg). Serum posaconazole levels were 4.3 - 4.6 μg/mL and itraconazole and hydroxyitraconazole concentrations were 2.11 μg/mL and 2.83 μg/mL. Complete suppression of renin and aldosterone, with increased 11-deoxycortisol, estradiol levels and cortisol/cortisone ratios were observed in all patients. Additionally, the transtubular potassium gradient (TTKG) was inappropriately elevated.

Results
The mechanism of itraconazole or posaconazole induced disruption of the steroid biosynthesis pathway in patients has not previously been described, but has been suggested by *in vitro* studies. Our patients' laboratory results show clinically significant inhibition of 11β-hydroxysteroid dehydrogenase enzyme type 2 isoform (11β-HSD2) as evidenced by: the elevated 11-deoxycortisol (with subsequent suppression of renin and aldosterone), the highly elevated cortisol/cortisone ratio, and the inappropriately elevated TTKG in the setting of hypokalemia. The normal deoxycorticosterone confirms normal function of 11β–hydroxylase and the observed effects in our patients are thus downstream from this enzyme.

Conclusion
Our findings support *in vitro* predictions and highlight the clinical sequelae of itraconazole or posaconazole-mediated inhibition of 11β-HSD2. Additional studies are necessary to determine the frequency of triazole induced apparent mineralocorticoid excess (AME) syndrome and whether other azole antifungals can be associated with this phenomenon.

DELAYS IN DIAGNOSIS OF COCCIDIOIDOMYCOSIS IN TUCSON, ARIZONA

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Introduction Coccidioidomycosis (Valley Fever) is typically transmitted by inhalation of airborne spores of *C. immitis* or *C. posadasii*. More often than not, Valley Fever is diagnosed as community-acquired pneumonia (CAP) and treated as such, even in endemic areas (Arizona and California). Most patients infected with *Coccidioides* spp. are asymptomatic, or have a self-limited disease which requires only supportive care for many weeks or even months. Diagnosis and therefore appropriate management of early coccidioidomycosis depends on laboratory testing which can result in delays. Arizona Department of Health Services' published enhanced surveillance during 2007 suggests this is common. We believe that if this interval were reduced, patients would be managed more precisely, and unnecessary care could be eliminated. The purpose of this retrospective study is to determine the length of delay from patients first seeking medical care to laboratory diagnosis of coccidioidomycosis and to calculate total health care utilization during that period.

Methods We selected charts within a 12 month interval for which ICD9 &10 codes for coccidioidomycosis were first identified. Two physicians independently reviewed the records in the electronic medical record (EMR) and with > 98% agreement excluded non-adult patients without a laboratory confirmed new coccidioidal infection. For the remaining records, the date was identified of first medical visit for syndromes consistent with an illness subsequently determined to be coccidioidomycosis. These syndromes were categorized by type: 1) symptomatic pulmonary infection or related immunologic response (rash, arthralgia, fatigue); 2) extrapulmonary progressive infection; 3) fibrocavitary chronic pulmonary infection; 4) asymptomatic pulmonary nodules. We then calculated the number of days from first visit until diagnosis and applied a cost analysis to that interval. Outpatient costs were calculated using Medicare Fee Schedules and inpatient costs were calculated using California per diem (Sondermeyer, EID 2013).

Results Of the 360 charts reviewed, 142 charts (40%) met inclusion criteria. Of these, 31% had a delay in diagnosis of ≥30 days. 12 patients, 8% (14 admissions, total 54 days) were hospitalized before diagnosis. Total antibiotic days were 504, with an average of 23 days per patient. Most commonly used antibiotics were Fluoroquinolones 23%, Vancomycin 20%, Ceftriaxone 6%, and Azithromycin 7%. Median (total) costs for outpatient were $1,400 ($148,944). The inpatient total cost was $367,200. The overall estimated cost before diagnosis was approximately $3,634 per patient.

Conclusion From an EMR review, we confirmed a significant delay in Valley Fever diagnosis in an area highly endemic for the disease. Not identified in our estimates are an unknown number of additional patients who had similar illnesses due to coccidioidal infection but who were never correctly diagnosed. Diagnostic delays resulted in unnecessary antibiotic use and misdirected healthcare expenses. We hope that the results from this and future studies provide the basis for effective interventions to reduce the interval in diagnosis of Valley Fever.

RAPIDITY OF COCCIDIOIDOMYCOSIS DIAGNOSIS AND ITS EFFECT ON HEALTHCARE UTILIZATION

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Introduction Coccidioidomycosis (CM) is a fungal infection caused by *Coccidioides* spp., common to parts of the Western Hemisphere, with Arizona representing over two-thirds of U.S.-based cases. Distinguishing CM from other causes of community-acquired pneumonia, or other presenting syndromes, requires specific laboratory tests—without which, misdiagnosis and delays in appropriate management often lead to ineffective, costly, and unnecessary care. Understanding these early processes better might identify opportunities for improving future clinical practice.

Methods This study was conducted at Banner University Medical Center-Phoenix, in conjunction with access to Banner Health's ambulatory (NextGen) and hospital-based (Cerner) electronic medical records (EMRs). In Phase 1, we identified free-text CM symptoms, via manual chart review in a random subset of patients diagnosed with CM. Two clinicians identified the symptoms through independent agreement. In Phase 2, we intended to use ICD-9 codes for those symptoms, to computationally index the onset of illness in a larger set of patients. However, the ICD-9 codes from Phase 1 were overly specific for extraction within an EMR system. Thus, two clinicians and a medical student reviewed the patient history for symptom codes clinically similar to the Phase 1 list. This resulted in an expanded set of symptoms. For Phase 2, adult patients were extracted from the ambulatory clinics' EMR database (N=139), which had an ICD-9 code for CM and confirmatory serologic tests. Health care utilization (total charges) were determined for the diagnostic delay [time from initial symptom date to initial (index) CM diagnosis date] and for the six months after the index date.

Results For Phase 2, we expanded the Phase 1 ICD-9 symptom codes from 23 to 89, which permitted assigning an initial symptom date in 120 of 139 patients. The median and total costs for 56 patients, with 0-30 days of delay, was $770 and $351,303, respectively. For the 10 patients, who had the highest delay category of 151-183 days, the median and total costs were $8,917 and $577,236, respectively. Of the 120 patients with a symptom date, the remaining 54 fell into intermediary delay buckets. The total healthcare charges for all patients (including those without symptoms) was $2,841,254. A small final population size precluded meaningful statistical analysis.

Conclusion Currently, there are few studies examining the consequences of CM diagnosis delay on healthcare utilization, and there are no tools available to identify symptoms of CM programmatically within EMR systems. In this pilot study, we have developed a prototype routine to do that. The results show large diagnostic delays and associated health care costs in CM patients. Future work could pave the path for larger, statistically robust studies, or future clinical decision support tools. Our findings support the continued study of this problem, and potential ways to reduce diagnostic delays.

ANTIBIOTIC AND ANTIFUNGAL TREATMENT AMONG PATIENTS WITH COCCIDIOIDOMYCOSIS IN SOUTHERN CALIFORNIA 2011

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Background

Coccidioidomycosis, caused by inhaling *Coccidioides* spp. fungi, can cause respiratory symptoms commonly mistaken for bacterial pneumonia and progress to severe disseminated disease. Antibiotics are ineffective in treating coccidioidomycosis, whereas antifungals are essential for treating severe disease. We investigated coccidioidomycosis testing and treatment patterns in an integrated health care delivery system to identify gaps in the diagnosis and treatment of this neglected disease.

Methods

We identified persons with coccidioidomycosis diagnoses during 2011 using Kaiser Permanente Southern California electronic health records. Cases were confirmed by positive complement fixation or immunodiffusion antibody test, culture, or histological report identifying *Coccidioides*. To analyze complex longitudinal events (antibiotic and antifungal treatments), we used EventFlow to identify sequences and time between events before and after first positive coccidioidomycosis test. We included antifungals given ≤1 year after and antibiotics given ≤3 months before and after date of coccidioidomycosis testing.

Results

Among 530 patients with confirmed coccidioidomycosis, 77% received antibiotics ≤3 months before or after first positive test; 80% received antifungals during the year before or after first positive test. Among those treated with antibiotics, the majority (70%) received antibiotics before their first positive test; among those with antifungals, 79% received them ≤1 year after first positive test. For patients receiving antibiotics before positive tests, median time between the 2 events was 12 days (interquartile range = 2–33 days), and 74% received >1 antibiotics course before positive tests. The most common event sequence (35%) was antibiotic treatment followed by positive test and then antifungal treatment.

Conclusion

Most patients received antibiotics before their coccidioidomycosis test, with many receiving multiple antibiotics courses and experiencing diagnosis delays. Positive coccidioidomycosis tests led to markedly lower rates of antibiotic treatment and to the initiation of antifungal treatment. Clinicians in coccidioidomycosis endemic regions including California should consider expanding coccidioidomycosis testing to reduce unnecessary antibiotic use and guide correct treatment.

Case Reports

Neil Ampel, Moderator

COCCIDIOIDOMYCOSIS OF THE EPIDIDYMIS AND TESTIS PRESENTING AS A TESTICULAR MASS
Sheikhan Nazanin, Heidari Arash, Hillyer Shahab (CSG-39)

COCCIDIOIDAL MENINGITIS WITH VASCULITIC MYCOTIC ANEURYSMS: A CASE AND REVIEW
D'Assumpcao C, Kaur S, Chen J, Johnson R, Heidari A (CSG-28)

COCCIDIOIDOMYCOSIS CHORIORETINITIS
Nordstrom B, Heidari A, Johnson R H, Chawla A (CSG-32)

SALVAGE THERAPY WITH ISAVUCONAZOLE FOR THE TREATMENT OF COCCIDIOIDAL MENINGITIS: A CASE REPORT
Ngai T, Mu A (CSG-2)

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COCCIDIOIDOMYCOSIS OF THE EPIDIDYMIS AND TESTIS PRESENTING AS A TESTICULAR MASS

Sheikhan Nazanin, Heidari Arash, Hillyer Shahab

Kern Medical – UCLA, Bakersfield, CA

Introduction

Coccidioidomycosis is endemic to the Southwestern United States and Northern Mexico. Most patients have primary Coccidioidomycosis with pulmonary involvement. Dissemination to the genitourinary system is very rare. We are reporting a case of dissemination to the epididymis, presenting as a testicular mass.

Methods

This is a retrospective review of medical records at Kern Medical. Patient's demographics, radiologic, serologic, pathologic, and laboratory results were reviewed.

Results

A 26-year-old Hispanic male with no medical history presented with a persistent right testicular mass, which initially manifested two years prior. He initially presented with urinary retention and was diagnosed with epididymitis and prescribed a course of levofloxacin. Following completion of antibiotics, patient had resolution of his urinary retention but the right testicular swelling persisted. The patient sought medical care two years later. An ultrasound revealed a heterogeneous prominent right epididymis with multiple hypoechoic cysts and a small right hydrocele. Due to concern for a neoplasm, the patient was referred to our facility for urological evaluation. Testicular tumor markers were negative. A repeat ultrasound revealed two exophytic and contiguous hypoechoic masses in the right testis, with a small amount of vascularity within these nodules. Subsequently, the patient underwent a right radical orchiectomy. Gross surgical pathology revealed two cystic cavitary lesions (Image 1); one in the inferior portion of the testis and one involving the epididymis. Biopsy showed no evidence of malignancy. However, fungal stain was consistent with *Coccidioides* spherules with endosporulation. Later, *Coccidioides* serology showed positive immunodiffusion IgG and complement fixation of 1:8. The patient was started on fluconazole 800 mg daily. The patient revealed that after he had relocated to the San Joaquin Valley three years prior. He was diagnosed with a self-limited pulmonary infection characterized by fever, rigor, cough, and target-like rash on his chest and abdomen.

Image 1: Demonstrates two cystic cavitary lesions; one in the inferior portion of the testis and the other involving the epididymis.

Conclusion

We present a rare case of male genitourinary coccidioidomycosis in an immunocompetent host. This case demonstrates the importance of considering fungal infections in the differential diagnosis of a focal testicular mass or swelling, especially when located in areas endemic to certain fungal infections. Recognition of such infections in a timely manner would yield prompt treatment with systemic antifungal therapy, surgical resection, and reduced morbidity.

COCCIDIOIDAL MENINGITIS WITH VASCULITIC MYCOTIC ANEURYSMS: A CASE AND REVIEW

D'Assumpcao Carlos, Kaur Simmerdeep, Chen Joseph, Johnson Royce, Heidari Arash

Kern Medical – UCLA, Bakersfield, CA

Introduction

Meningitis is the most feared form of disseminated coccidioidomycosis. Cerebral vasculitis occurs in approximately 10% of meningitis cases. Coccidioidal mycotic aneurysms has only been reported in four published cases. We herein describe a fifth case.

Case Summary

26 year old Latino man developed persistent occipital headache with associated fever, nausea, and vomiting. At an institution prior to Kern Medical, he was found to have a pulmonary cavitary disease and cerebrospinal fluid (CSF) consistent with chronic meningitis and so fluconazole 800mg and dexamethasone 4mg taper was started.

Three weeks later, he presented to Kern Medical with headaches, fever, nuchal rigidity and photophobia. CSF demonstrated WBC 200 with 75% lymphocytes, glucose 10, and protein 86 with negative immunodiffusion and immunofixation but CSF culture grew *Coccidioides* species. Imaging demonstrated a left basilar ganglia enhancement. Fluconazole 1000 mg and dexamethasone were restarted and he was discharged to follow up in Cocci Clinic in one month.

Headache, nausea and vomiting were intermittently persistent. Lumbar puncture performed at follow up had an opening pressure of 300 mmH_2O. He was readmitted. Imaging revealed a new right basilar coccidioma. Therapy was changed to itraconazole 200 mg every 12 hours. Intracranial pressures appeared to stabilize and he was discharged.

Two weeks later, he fell out of bed, per family. He developed a severe headache and returned to the Emergency Department. Imaging found a left subarachnoid hemorrhage and a left middle cerebral artery (MCA) aneurysm. He was transferred to another institution for neurovascular surgery.

He underwent a left pterional craniotomy with superficial temporal artery to MCA bypass graft and clipping of the left distal MCA aneurysm with excision. Pathology found fungal hyphae and spherules with endospores in the arterial wall, vasculitis, fragmentation of the elastic lamina, and disrupted media.

Post-operatively, he suffered a left MCA distribution infarction and developed generalized seizures. Repeat CT angiography found new multiple aneurysms. Voriconazole and liposomal amphotericin B were started. Intra-arterial verapamil was infused almost daily for cerebral vasospasms. A ventricular peritoneal shunt was placed for hydrocephalus. After thirty days, he was transferred back to Kern Medical for continuation of care.

Outcome

Aphasia and right hemiparesis remained. Unfortunately, he failed to improve. He went home with family on hospice, where he died six months after initial symptom onset.

Conclusion

To our knowledge, this is the fifth reported case of coccidioidal mycotic aneurysms. It was associated with subarachnoid hemorrhage and cerebral arterial vasospasm.

COCCIDIOIDOMYCOSIS CHORIORETINITIS

Nordstrom Brian, Heidari Arash, Johnson Royce H, Chawla Anuj

Kern medical, Bakersfield California

Introduction

Disseminated coccidioidomycosis occurs in approximately 1% of infected patients. Seeding of the eye is uncommon. When ocular involvement is present it most commonly affects the conjunctiva and the anterior segment structures. Cases of Iridocyclitis have been reported. Isolated choroid and/or vitreal disease are even less common. To our knowledge only 6 cases of primary chorioretinitis have been reported in patients with disseminated disease. The majority of these cases were reported without vitreal involvement or arose status post vitrectomy. Our case is a rare presentation of chorioretinitis with vitreal involvement.

Case Summary

27 year old Filipino man presented to Kern Medical with decreased vision in his left eye, low back pain, weakness in his lower extremities, and masses in his paraspinal, supraclavicular, and submandibular regions. Thoracic and abdominal CT demonstrated multiple abscesses with involvement of the left supraclavicular lymph nodes and a left paraspinal abscess extending from T7 -T12 with penetration and subsequent osteomyelitis of the T12 vertebra. Whole body bone scan also showed increased uptake of left fibular and tibial regions, left frontal lobe, and xiphoid process. Incision and drainage of the paraspinal abscess and subsequent staining of the aspirate indicated the presence of double walled spherules with endosporulation. Serological immunodiffusion showed IgM and IgG reactivity with a complement fixation titer of ≥ 1/512. The patient was placed on liposomal amphotericin B for his extraocular disease.
The patient started to complain of floaters in his left eye, which progressed until he complained of a total loss of vision in this eye. Ophthalmologic examination discovered “puff balls” in the vitreous overlying the posterior pole in this eye only. The right eye did not have any abnormal findings. He was discharged from the hospital and referred to a retinal specialist as an outpatient. On examination he had normal visual acuity in the right eye, with light perception vision only in the left eye. Anterior segment exam did not reveal an active anterior uveitis. In the left eye there were found to be significant vitreous opacities. A large, white subretinal lesion was present in the temporal macula. There was significant traction associated with this lesion and a combined tractional/exudative retinal detachment was present, extending inferiorly. Given the history of concurrent coccidioidomycosis infection, the patient was diagnosed with a coccidiomycosis associated chorioretinitis. He was started on intravitreal amphotericin B deoxycholate 5mcg/0.1 mL every three days in addition to his systemic treatment.

Conclusion

Although rarely seen, ocular coccidioidomycosis must be considered in patients with a compatible clinical presentation. Any patient with coccidioidomycosis that has new or unexplained eye symptoms should be immediately referred to an ophthalmologist for examination. Recommended treatment includes vitrectomy and intravitreal amphotericin B deoxycholate. Most patients will be left with extensive choroidal and retinal scarring. Coccidioidomycosis endophthalmitis portends a poor prognosis for vision and often eventuates in enucleation.

SALVAGE THERAPY WITH ISAVUCONAZOLE FOR THE TREATMENT OF COCCIDIOIDAL MENINGITIS: A CASE REPORT

Ngai, Tiffany; Mu, Anandit
Division of Infectious Diseases, University of California San Francisco - Fresno

Introduction Fluconazole has demonstrated efficacy in treatment of coccidiodal meningitis (CM). For infections refractory to fluconazole, voriconazole is an effective alternative agent. However, adverse effects can limit its use. Isavuconazole has shown activity against pulmonary coccidioides, and studies in cryptococcal meningitis have proven its efficacy in treatment of central nervous system (CNS) infections.

Case Summary A 43-year-old male was diagnosed with CM in 2007. Despite high dose fluconazole, he had persistent headaches with hydrocephalus requiring a ventriculoperitoneal shunt in 2008. He was transitioned to voriconazole which was tolerated well. Cerebrospinal fluid (CSF) remained positive for IgG by immunodiffusion (ID) but negative by complement fixation (CF). By 2013, he was experiencing photosensitivity with multitudinous cutaneous lesions from voriconazole. In 2017, biopsies revealed squamous cell carcinoma. Although data on CNS penetration are limited, voriconazole was changed to isavuconazole. Three months later, CSF was negative for coccidioides by ID and CF.

	Serum ID	Serum CF	CSF ID	CSF CF
2006	Positive IgM and IgG	1:2	Negative	
Started on fluconazole, unknown initial dose				
2007	Positive IgG	1:2		1:4
February 2007 Started on fluconazole 600mg PO BID				
2008	Positive IgG	1:2	Positive IgG	Negative
April 2008 Ventriculoperitoneal shunt placed and started on voriconazole 200mg PO TID				
2009	Positive IgG	Negative	Positive IgG	Negative
2010	Positive IgG	Negative		
2010-2016	Positive IgG	Negative		
February 2017 Started on isavuconazole 372mg PO TID x 2 days then 372mg PO daily				
May 2017	Positive IgG	Negative	Negative	Negative

*ID = Immunodiffusion
*CF = Complement Fixation
*CSF = Cerebrospinal Fluid

Discussion Murine studies have shown high brain tissue to plasma concentrations of drug which decreased fungal burden of infections such as cryptococcus. The VITAL trial described lower minimum inhibitory concentrations of isavuconazole compared to fluconazole for a number of fungal infections. Although the VITAL trial studied cryptococcal memingitis, patients were successfully treated. This demonstrated the potential of isavuconazole as salvage therapy. Isavuconazole may show utility for other fungal CNS infections, including CM.

Conclusion We report a case of CM that failed treatment with high dose fluconazole and developed widespread cutaneous squamous cell carcinoma on voriconazole. The disease is now successfully controlled with isavuconazole, making this the first human report of isavuconazole's efficacy in treatment of CM. Animal studies of the pharmacokinetics of isavuconazole in the CNS are promising for therapy in CM.

Business Meeting - NEIL AMPEL, Presiding

I. Nominations for outgoing Board Officers by Janis Blair (floor nominations are ok)

- Program Director: open
- Treasurer: Royce Johnson
- Nominations Chair: Janis Blair
- Web Site Chair: Jessica Einstein
- Veterinary Representative: Lisa Shubitz, Autumn Davidson

II. CSG-63 (2019) meeting site: U.C., Davis-Sacramento. George Thompson III will host.

III. CSG-64 (2020) site: Phoenix, Tucson, New Mexico or San Antonio, TX. Host TBD.

IV. Treasurer's Report: Royce Johnson

V. Announcements

President's award for Performance Excellence goes to: **Karl V. Clemons, Ph.D.**

Travel Grant award goes to: **Jisha Joshua, M.D.**

VI. Update on Community Acquired Pneumonia (CAP) by Carmelle Norice-Tra representing the National Institutes of Allergy and Infectious Diseases (NIAID)

VII. Other New Business

VII. Board of Directors meeting will be at 5:00 today, to include newly elected members. CSG Banquet at 7:00 is by reservation at Restaurant 1899.

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Co-Hosts for CSG-62 in Flagstaff, Arizona

BRIDGET BARKER JOEL TERRIQUEZ

Program Committee

Bridget Barker
Janis Blair
Herbert Boro - Chair
Karl Clemons
Susan Hoover
Orion McCotter
Heather Mead
Natalie Mitchell
Lisa Shubitz
Rebecca Sunenshine

Board of Directors

Neil Ampel - Chair
Bridget Barker
Janis Blair
Herbert Boro
Antonino Catanzaro
Autumn Davidson
Jessica Einstein
Royce Johnson
Rafael Laniado-Laborin
Rebecca Sunenshine
George Thompson III

AWARDS AND HONORS – 1957-2018

1957 **Myrnie Gifford** for her fundamental contributions to our understanding of coccidioidomycosis.

1967 **Charles E Smith** for his medical insight, investigational genius, and boundless enthusiasm.

1984 **Robert W. Huntington** and **Milton Huppert** and for their dedication to the understanding of coccidioidomycosis

1996 **Hans Einstein, Hillel Levine, Demosthenes Pappagianis** and **David Salkin**, for their contributions to the field of coccidioidomycosis

2001 **John Galgiani** for Lifetime Achievement Award in appreciation of 15 years of valuable and dedicated service as Cocci Study Group Secretary

2007 **Antonino Catanzaro** for the Emmet Rixford Lifetime Achievement Award; **David A. Stevens** for the Charles E. Smith lifetime achievement award.

2016 **Antonino Catanzaro** in appreciation of 10 years of dedicated service as Cocci Study Group President

2017 **Neil Ampel, Janis Blair** and **Royce H. Johnson** for CSG Lifetime Achievement Awards

2017 **Herbert Boro** and **Rafael Laniado-Laborin** for CSG President Achievement Awards

2018 **Karl V. Clemons** for CSG President Achievement Award for the Consistent Performance of Excellence

Annual Meetings of the Coccidioidomycosis Study Group

No.	Date	Location	Held in Conjunction with
1	July 18, 1956	San Francisco, CA	Seminal Meeting
2	December 5-6, 1957	Los Angeles, CA	-
3	December 4-5, 1958	Los Angeles, CA	-
4	December 3-4, 1959	Los Angeles, CA	-
5	December 8-9, 1960	Los Angeles, CA	-
6	November 30-December 1, 1961	Los Angeles, CA	-
7	November 29-30, 1962	Los Angeles, CA	-
8	December 5-6, 1963	Los Angeles, CA	-
9	December 10-11, 1964	Los Angeles, CA	CA Thoracic Society
10	December 7, 1965	Phoenix, AZ	2nd Cocci Centennial Conference
11	April 19, 1967	Palm Springs, CA	CA Thoracic Society
12	May 1, 1968	Fresno, CA	CA Thoracic Society
13	April 15, 1969	San Diego, CA	CA Thoracic Society
14	April 1, 1970	San Francisco, CA	CA Thoracic Society
15	April 6, 1973	Newport Beach, CA	CA Thoracic Society
16	April 5, 1974	Sacramento, CA	CA Thoracic Society
17	September 30, 1974	San Francisco, CA	Cocci Cooperative Treatment Group
18	April 2, 1975	San Diego, CA	CA Thoracic Society
19	July 31, 1975	San Diego, CA	Cocci Cooperative Treatment Group
20	January 14-15, 1976	San Diego, CA	Cocci Cooperative Treatment Group
21	April 7, 1976	Palo Alto, CA	CA Thoracic Society
22	May 18, 1977	San Francisco, CA	Am Lung Association
23	April 5, 1978	Beverly Hills, CA	CA Thoracic Society
24	May 15, 1979	Las Vegas, NV	Am Lung Association

No.	Date	Location	Held in Conjunction with
25	April 11, 1980	Sacramento, CA	CA Thoracic Society
26	March 28, 1981	San Francisco, CA	CA Thoracic Society
27	May 15, 1982	Los Angeles, CA	AM Lung Association
28	March 20, 1983	La Jolla, CA	CA Thoracic Society
29	March 14-17, 1984	San Diego, CA	4th Cocci Centennial Conference
30	March 8, 1986	Santa Barbara, CA	-
31	April 4, 1987	Los Angeles, CA	-
32	April 9, 1988	Los Angeles, CA	-
33	April 8, 1989	San Jose, CA	-
34	April 7, 1990	Berkeley, CA	-
35	April 6, 1991	Tucson, AZ	-
36	April 4, 1992	Fresno, CA	-
37	April 3, 1993	Tucson, AZ	-
38	August 24-27, 1994	Stanford, CA	5th Cocci Centennial Conference
39	April 1, 1995	Bakersfield, CA	-
40	March 30, 1996	Scottsdale, AZ	-
41	March 5, 1997	San Diego, CA	-
42	April 4, 1998	Visalia, CA	-
43	March 20, 1999	Tijuana, BC, Mexico	-
44	April 1, 2000	Berkeley, CA	-
45	March 31, 2001	Tucson, AZ	-
46	April 6, 2002	Davis, CA	-
47	April 3, 2003	Scottsdale, AZ	-
48	April 31, 2004	Rosarito Beach, Mexico	-
49	April 2, 2005	Bass Lake, CA	-
50	April 23-26, 2006	Stanford, CA	6th International Symposium on Cocci
51	March 29, 2007	Tempe, AZ	-

No.	Date	Location	Held in Conjunction with
52	April 5, 2008	San Diego, CA	-
53	April 4, 2009	Bakersfield, CA	-
54	March 27, 2010	Surprise, AZ	-
55	April 2, 2011	Davis, CA	-
56	March 24, 2012	Tucson, AZ	-
57	April 6, 2013	Pasadena, CA	-
58	April 5, 2014	Phoenix, AZ	-
59	April 11, 2015	San Diego, CA	-
60	April 8-9, 2016	Fresno, CA	-
61	August 10-13, 2017	Stanford, CA	7th International Cocci Symposium
62	April 13-14, 2018	Flagstaff, AZ	-

Important Internet Web Sites

- **The Cocci Study Group – sponsor of the annual valley fever scientific meeting - site of archived CSG Proceedings**

The Coccidioidomycosis Study Group was created in San Francisco, California on July 18, 1956. This group oversees conferences, annual meetings and research studies. Much of the documented knowledge of the pathogenesis, mycology and clinical aspects of Coccidioidomycosis originated from studies performed by this research group. The web site is a repository for recent Annual CSG meeting abstracts. **www.coccistudygroup.com**

- **The Valley Fever Center for Excellence – site of archived CSG Proceedings**

The Valley Fever Center for Excellence, located at the University of Arizona in Tucson, was established to address the problems caused by the fungus, *Coccidioides*, the cause of coccidioidomycosis (Valley Fever). Two-thirds of all *coccidioides* infections in the United States occur in Arizona, mostly in the urban areas surrounding Phoenix and Tucson. The Center's mission is to mobilize resources for the eradication of Valley Fever (Coccidioidomycosis) through: 1) the development of public awareness and education about Valley Fever, 2) the promotion of high quality care for patients with Valley Fever, and 3) the pursuit and encouragement of research into all aspects of *Coccidioides sp*. and the diseases that it causes. The web site is a repository for most of the Annual CSG meeting abstracts.
www.vfce.arizona.edu

- **Valley Fever Americas Foundation**

The Valley Fever Americas Foundation (VFAF) was founded by Rotary Clubs in 1995 to promote research for the cure for Valley Fever. **www.valleyfever.com**