PROCEEDINGS OF THE 63RD COCCIDIOIDOMYCOSIS STUDY GROUP ANNUAL MEETING

April 5–6, 2019

University of California Davis Medical Center

Sacramento, CA

ECOLOGY

DETECTION AND CHARACTERIZATION OF ONYGENALEAN FUNGI ASSOCIATED WITH PRAIRIE DOGS IN NORTHERN ARIZONA

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Background: Onygenalean fungi include a broad array of species associated with animals and their surrounding habitats. Burrowing-mammal species may contribute to their maintenance because burrows are enriched with animal-derived material such as feces, fur, and decomposing carcasses. Prairie dogs (PD) are comprised of at least five *Cynomys* species native to western North America and northern Mexico, overlapping the range of coccidioidomycosis. We hypothesize that PDs may be one host of *Coccidioides* spp., and these animals may facilitate fungal maintenance and dispersion.

Methods: 16 *C. gunnisoni* specimens were collected from Aubrey Valley, Seligman, AZ, USA. The lungs were split into quarters, and sample from each quarter was used for DNA extraction. A subset of the remaining quarters were used for culturing. The mycobiome of PD lungs was assessed using ITS2 amplification followed by metagenome sequencing. ITS2 sequences were analyzed using Qiime 1.0 software and Ghost tree methods. Fungal isolation was carried out by plating homogenized lung tissue onto agar plates incubated at 24°C and 37°C for 4 weeks. 48 colonies were picked to single colonies and genotyped by sequencing entire ITS region, and 25 of these were fully sequenced for phylogenomic comparisons.

Results: The percentage of Onygenales-specific OTUs detected in PD lungs was as high as 21.40%. 12 samples were Onygenales-positive and harbored relevant pathogens such as *Emmonsia* spp., *Coccidioides posadasii* and *Blastomyces dermatitidis*. Ghost-trees were created using a 4-loci alignment as a backbone, and revealed that those OTUs likely belong to the Ajellomycetaceae and Onygenaceae families. We isolated 48 fungal colonies from PD lungs, and using full ITS sequencing, 25 were typed as Onygenales, which included *Emmonsia*, *Chrysosporium*, *Auxarthron,* and Onygenales sp. WGS of 9 of these strains confirmed the existence of new Onygenalean taxa associated with PD.

Conclusions: We propose that PDs are natural hosts for Onygenalean fungi, which may be reservoirs for human fungal pathogens. We provide evidence that massively parallel ITS2 sequencing is an efficient pipeline for pathogen discovery and ecological studies and should be further explored. Moreover, microbiological and molecular techniques are important and needed to evaluate genomes of monosporic isolates.

ENVIRONMENTAL NICHE MODELING OF *COCCIDIOIDES* SPP. IN WASHINGTON STATE

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INTRODUCTION

In 2013, *Coccidioides* spp. was detected in soils from Washington (Litvintseva et al. 2014), well outside the previously thought endemic range of the southwestern US. Previous work from Gorris et al. found counties with a mean annual temperature above 10.7°C and mean annual precipitation below 600 mm/yr represent the coccidioidomycosis endemic area from the Centers for Disease Control and Prevention with good agreement. This model successfully highlights three counties in Washington as potentially endemic for valley fever: Benton, Franklin, and Walla Walla. Our goal is to downscale and improve this climate-constrained threshold model to identify a more precise area endemic to coccidioidomycosis in Washington.

METHODS

To improve our threshold model, we are using the Maxent software for modeling species distributions and niches via a maximum entropy model. As input, we use climate data from PRISM Climate Group at Oregon State, including mean annual temperature and mean annual precipitation at a 4 km^2 resolution. We are expanding our model to include soil characteristics from the US Geographical Survey, including pH and soil grain size. To evaluate our model, we have 95 soil samples positively identified with *Coccidioides* spp. within southeastern Washington State. As a separate measure of model performance, we plan to include canine serology samples georeferenced to the county level.

RESULTS

Our downscaled climate threshold model (4 km^2) successfully identifies all 95 occurrence data as potentially endemic and includes the majority of Benton, Franklin, and Walla Walla Counties; portions of Grant, Yakima, Klickitat, Adams, Columbia, Garfield, Whitman Counties; and small areas within Chelan, Douglas, Kittitas, and Asotin Counties. Our preliminary Maxent model results using mean annual temperature and mean annual precipitation as input identified eastern Kittitas, eastern Yakima, southeastern Klickitat, Grant, Benton, southwestern Adams, Franklin, and northwestern Walla Walla Counties as endemic.

CONCLUSION

Our environmental niche model of *Coccidioides* spp. in Washington State will be used by the Washington State Department of Health for future soil sampling campaigns. Results from these additional soil sampling campaigns will help evaluate the performance of our model. Adding soil characteristics into our model will further refine the niche for *Coccidioides* spp.

EXPANDING THE MOLECULAR DETECTION TOOLKIT FOR *COCCIDIOIDES* BY DOCUMENTING GENETIC VARIATION FROM PATIENTS TREATED IN NEW MEXICO AND TESTING ENVIORNMENTAL SAMPLES

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Introduction. Coccidiomycosis is a disease of humans and animals caused by species of the dimorphic fungus *Coccidioides*. The disease is highly endemic to arid regions of the southwestern United States including California and Arizona, but it is also present in neighboring New Mexico, where it has been poorly studied. We are taking a multifaceted approach to study the distribution and ecology of species of *Coccidioides* in New Mexico. These approaches include the characterization of isolates obtained from human infections, efforts to expand the methods available to detect low levels of *Coccidioides* DNA in tissues and environmental samples, and the development of PCR-based methods to distinguish between *C. immitis* and *C. posadasii*.

Methods. Eighteen clinical isolates were obtained by the New Mexico Department of Health, Scientific Laboratory Division from patients diagnosed with coccidioidomycosis. Patient and geographic information was available for several isolates. A multi-gene phylogenetic analysis was performed. In separate experiments, regions of the mitochondrial genome were explored to identify PCR primer targets specific for the genus *Coccidioides* or for one of the two species.

Results. Genetic analysis of isolates from New Mexico and the Four Corners region revealed that both *C. posadasii and C. immitis* are present in the region. Five of eight infections for which patient ethnicity was known occurred in Native Americans, and two occurred in African Americans. Several of the isolates came from northwestern New Mexico outside the predicted "highly-endemic" region. We have been able to design a primer pair with one primer targeting an indel in mtDNA that results in amplification of a sequence in *C. posadasii* but not *C. immitis*. In addition, a separate primer pair has been designed to amplify sequences from both species of *Coccidioides* but not other Onygenales. The latter primer pair has been used to amplify DNA extracted from soil known to harbor low amounts of *C. immitis*.

Conclusions. This study provides a foundation for future exploration of the geographic distribution of the two causative agents of coccidioidomycosis, *C. posadasii* and *C. immitis*, and for predicting and preventing exposure among populations at risk in the region.These molecular approaches have potential to aid in accurate, timely, and cost-effective diagnosis.

EXPANDING THE KNOWN DISTRIBUTION OF COCCIDIOIDES IN WASHINGTON STATE THROUGH ONE HEALTH SURVEILLANCE

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INTRODUCTION

Ongoing surveillance for *Coccidioides* in Washington contributes to knowledge of public health risk and habitats for pathogen persistence. A One Health approach to *Coccidioides* surveillance includes performing follow-up environmental investigations on potential exposure locations of human and animal cases, environmental surveillance based on niche model predictions, and canine serology surveys as a proxy method for estimating geographic areas of increased risk.

METHODS

We performed environmental investigations in collaboration with local health jurisdictions to identify potential exposure sites based on case-patient interviews. Environmental investigations were targeted to areas where outdoor activity and dust exposure occurred. In 2015 and 2016, we conducted two environmental investigations in Benton and Yakima Counties. For both investigations, we collected soil samples from areas where soil-disturbing activity took place. Environmental surveillance between 2015 and 2018 was conducted in Benton, Kittitas, Walla Walla, and Yakima Counties. Over 500 samples were collected from 11 localized sites chosen based on two niche models: one modeled a habitat similarity index using USDA-NRCS SSURGO data on soil characteristics compared to Southwest endemic regions and the second modeled a soil suitability index compared to *Coccidioides*-positive sites in Washington. Canine serology surveys were conducted in collaboration with 25 veterinary clinics in 17 counties between 2014 and 2018. Over 1200 canine serum samples were collected and tested for presence of *Coccidioides* IgG antibodies.

RESULTS

Environmental investigations in Benton and Yakima Counties yielded positive detections of *Coccidioides* using the CocciDx qPCR assay. Environmental surveillance in Benton, Yakima, and Kittitas Counties yielded positive detections of *Coccidioides* from three localized sites. These five new localized sites with positive *Coccidioides* detections include three sites in Yakima and Kittitas Counties, where *Coccidioides* has not previously been reported from soils. Canine serology survey results indicate an average of 8% of canines sampled in Washington have been exposed to *Coccidioides*, with the majority of positive canines coming from Benton, Franklin, Yakima, and Walla Walla Counties.

CONCLUSION

Considering these additional environmental detections and canine serology data, it is likely that *Coccidioides* presents a risk to humans and animals across a larger region of central Washington than previously described and highlights a need for continued environmental surveillance.

EPIDEMIOLOGY

COCCIDIOIDES SKIN TESTING IN A COMMERCIALLY-INSURED POPULATION, UNITED STATES, 2014–2017

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INTRODUCTION: Historically, skin testing has been a valuable tool for estimating the prevalence of *Coccidioides* exposure and for monitoring treatment response in coccidioidomycosis patients. It could also be useful for evaluating healthy persons' risk for developing coccidioidomycosis. The skin test, approved for adults ages 18–64 with a history of coccidioidomycosis, became commercially available again in 2014; however, few recent data exist about its use in the general population.

METHODS: We used the IBM® MarketScan® Research Databases to identify patients with Current Procedural Terminology (CPT) code 86490 during 2014–2017. We analyzed demographic features, return visits within 3 days (compared with patients with a CPT code for tuberculosis skin testing [86580]), coccidioidomycosis diagnoses (ICD-9-CM codes 115.00–115.99 and ICD-10-CM code B38), serologic testing, and total cost to patients and insurers.

RESULTS: Among ~57 million unique MarketScan enrollees, we identified 505 patients who had a coccidioidomycosis skin test; 407 were continuously enrolled in the 3 months before and after the skin test. Of those, 243 (60%) were female, 361 (89%) were ages 18–64 years (median 46, range 2–85), 91% resided in California, and 4% resided in Arizona. Thirty-five percent had a return visit within 3 days, compared with 24% of those with a tuberculosis skin test. In the 3 months before the skin test, 5% had a coccidioidomycosis diagnosis, and 5% had a coccidioidomycosis serologic test. On the day of the skin test and in the 3 months after, 7% had a coccidioidomycosis diagnosis code, and 15% had a serologic test. Forty-four patients (11%) had non-capitated health plans; among those, mean cost of skin test claims was $43.66 (median $50.90, range $0–$264).

CONCLUSION: The skin test appears to be used uncommonly in this population. Patient age and return visit rate were consistent with the test's indication. However, few patients recently had coccidioidomycosis diagnosis codes, possibly suggesting screening for immunity in people with unknown exposure to *Coccidioides*, which has not been evaluated. Future studies to understand features of tested patients and clinicians' knowledge and attitudes could provide insight into how the test could be more widely used.

Coccidioidomycosis in U.S. residents returning from house-building trips in Baja California, Mexico, June–July, 2018

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Background: On August 8, 2018, New York City health authorities notified CDC of two high school students hospitalized following house-building trips to Baja California, Mexico. By October 15, 2018, both students and six additional travelers were diagnosed with coccidioidomycosis, a disease caused by inhalation of a soil-borne fungus found in parts of the U.S. and Mexico. A seroepidemiologic survey was conducted to identify potential sources and inform prevention measures.

Methods: We identified 209 people who traveled to the area during June–July 2018, performed serum *Coccidioides* antibody testing (lateral flow assay and enzyme immunoassays), and conducted interviews in person or by online questionnaire. Interviews included questions on activities, exposures, symptoms, and prior knowledge of coccidioidomycosis.

Results: We interviewed 109 (52%) travelers, of whom 48 (44%) reported coccidioidomycosis symptoms. Among 75 with antibody testing, 13 (17%) were seropositive, of whom 12 (92%) were symptomatic. Fourteen (29%) with symptoms sought healthcare, and four were hospitalized, including one in intensive care, for a median of seven days (range 3–12). Travelers who worked on a particular house (odds ratio [OR] 5.7, 95% confidence interval [CI] 1.2–54.9), performed backfilling of the foundation (OR 2.8, 95% CI 1.1–7.4), or took no precautions against dust generation (OR 9.4, 95% CI 1.3–424.1) had higher odds of developing symptoms compared with those who did not perform such functions. Only six (6%) travelers had ever heard of coccidioidomycosis.

Conclusion: Almost one in five travelers Baja California, Mexico showed serological evidence of coccidioidomycosis infection, and over one-third exhibited symptoms compatible with coccidioidomycosis, likely from foundation work at a particular house. Further investigation is needed to determine reasons this site posed elevated risk. Despite engaging in dust-generating activities in a coccidioidomycosis-endemic area, nearly all travelers were unaware of the risk. Service organizations performing soil-disturbing activities in endemic areas should educate travelers and implement prevention measures.

AN OBSERVATIONAL STUDY TO ASSESS THE PREVALENCE AND OUTCOMES OF PRIMARY PULMONARY COCCIDIOIDOMYCOSIS IN PERSONS AGED ≥ 14 YEARS PRESENTING WITH COMMUNITY ACQUIRED PNEUMONIA (CAP) IN ENDEMIC AREAS (SANDS-PPC)

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INTRODUCTION: Coccidioidomycosis occurs almost exclusively in the Southwestern United States. A multi-center study in Arizona and California to determine the prevalence of primary pulmonary coccidioidomycosis (PPC) among persons presenting with community acquired pneumonia (CAP), variations in treatment practices between regions, and predictors of a PPC diagnosis and disease severity at presentation was initiated in January 2019.

MATERIALS AND METHODS: This is a two-step prospective observational study. In Step 1, eligible persons (N=1,000) aged 14 years or older, with a CAP diagnosis and within 14 days of symptom onset, will be assessed sequentially over a 21-day period using local standard of care serologic tests to ascertain a PPC diagnosis. Persons determined to have acute PPC (within 14 days of serologic evaluation) as part of Step 1 or as part of routine care, will be referred to Step 2 (n=200), and followed for two years. Sequential evaluations will measure for pulmonary symptoms using a composite score; disease severity; disease dissemination; changes in radiographic findings; antifungal medication receipt; functional health and well-being; and participation in routine activities - school and work. Study procedures include physical examinations and serial coccidioidal serologies performed centrally.

RESULTS: Enrollment will continue through December 2021. The primary objective is to describe the proportion of persons with acute PPC among those presenting with CAP and elucidate demographic, clinical, and laboratory predictors of PPC. Among those with PPC, the following will be reported:

- Presence of pulmonary symptoms and disease severity at various time points
- Time to resolution of pulmonary symptoms
- Changes in initial chest radiographic findings
- Antifungal therapies prescribed
- Associations between the clinical course of PPC (as measured by the composite pulmonary symptom score, disease severity score and change in chest radiograph findings score) and antifungal treatment

Subjects receiving, and those not receiving, antifungal therapy for PPC will be compared according to the above scores, quality of life measures, time missed from school and work, disease dissemination, and mortality.

CONCLUSION: Upon completion this observational study will report PPC prevalence among patients with CAP in endemic regions, raising awareness of this condition. Assessments of PPC treatments and outcomes will inform future clinical practice.

COCCIDIOIDOMYCOSIS IN UTAH 2006-2015: EPIDEMIOLOGY, CLINICAL CHARACTERISTICS AND OUTCOMES

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INTRODUCTION

Coccidioidomycosis was first described in Utah in 1957. Based on Coccidioidin skin testing in volunteers, three counties in southwestern Utah were considered endemic – Iron, Kane and Washington counties. Since that time, there has been a paucity of information regarding the regional disease burden. We describe the epidemiology, clinical characteristics and outcomes of Coccidioidomycosis in Utah.

MATERIALS AND METHODS

We searched all encounters in the Intermountain Healthcare electronic medical record 2006-2015 for clinical data associated with Coccidioidomycosis. Each of the 788 potential cases of infection was reviewed manually. EORTC/MSG definitions were applied to categorize Coccidioidomycosis as proven or probable infection. Linear regression was used to model the incidence variation over time.

RESULTS

364 patients had serological, microbiological or pathological evidence of Coccidioidomycosis. 192 (52.7%) of cases were proven, and 172 (47.3%) were classified as probable. Mean incidence was 2.94 cases/100,000 patients per year and decreased by 0.09 cases/100,000 patients per year over the study period ($R^2 = 0.22$). Median age was 61 years with 55% of cases in males. The most common co-morbidities were chronic pulmonary disease (39.6%), diabetes mellitus (22.3%) and malignancy (20.9%). Primary pulmonary infection (86.8%) was the most common presentation; 3% had disseminated disease. 42% of cases clustered to three zip codes in Washington county. Preliminary climate and soil data suggest that number of soil frost-free days correlates with this geographic distribution. Many patients (30.2%) were diagnosed during hospitalization, and 28.6% were diagnosed during work-up for malignancy. All-cause mortality was 5.5% at 42 days and 9.1% at one year. An additional 115 patients living in the endemic regions of Utah were identified as having a positive IgG by ELISA without evidence of clinical disease. It is unclear if these cases represent remote or subclinical exposure with long lasting seropositivity, altering the current paradigm that the *Coccidioides* IgG should ultimately become negative over time.

CONCLUSION

Coccidioidomycosis is common in select areas of Utah and should be on the differential diagnosis for patients with pneumonia who spend time in endemic areas. Further work is needed to understand the cohort of patients with a persistently positive IgG by ELISA.

PRELIMINARY RESULTS OF A CASE-CONTROL STUDY OF COCCIDIOIDOMYCOSIS AMONG HISPANIC AGRICULTURAL WORKERS IN KERN COUNTY, CA

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INTRODUCTION: Coccidioidomycosis is an important public health problem in California, where there were 8187 suspected, probable, or confirmed cases reported in 2018, with the majority occurring in Kern and neighboring counties. Agricultural workers are at increased risk, yet there are few data examining whether specific crops or activities are associated with risk.

MATERIALS AND METHODS: We conducted a case-control study to look at occupational risk factors for coccidioidomycosis among adult Hispanic or Latino (self-identified) outdoor agricultural workers seen at Kern Medical county hospital and referred to the Kern County Department of Public Health Services Laboratory for coccidioidomycosis serological testing. Serologic evaluation comprised three tests: immunodiffusion for IgM and IgG and complement fixation (considered positive for dilutions $\geq$1:2). Persons with at least one positive serologic test were assigned case status, and persons with negative results for all three tests were assigned control status. Participants completed an interviewer-administered health and work history questionnaire focusing on agricultural employment activities in the preceding 12 months. We employed multivariable logistic regression to evaluate associations between case status and demographic characteristics, specific agricultural exposures, and clinical illness features.

RESULTS: There were 202 participants: 109 cases (64 men, 45 women) and 93 controls (41 men, 52 women). Median ages were similar for men and women cases and controls, ranging from 41.2 y (men controls) to 32.7 y (women controls). Cases and controls were comparable for country of birth (77% born in Mexico), completing interview in Spanish (85%), years lived in the US (median 18 y), and agricultural jobs in preceding year (median 3). Cases were significantly more likely than controls to report weight loss (median 10 vs. 0 lb, $p<0.01$), fever (65% vs. 30%, $p<0.01$), night sweats (66% vs. 37%, $p<0.01$), fatigue or weakness (83% vs. 55%, $p<0.01$), cough (67% vs. 39%, $p<0.01$), shortness of breath (60% vs. 27%, $p<0.01$), and lost work time (median 20 vs. 0 days, $p<0.01$).

CONCLUSION: Case status was strongly associated with clinical illness, including lost work time. Work is ongoing to assess the association between coccidioidomycosis risk and work and task exposures for specific crops.

VALLEY FEVER SURVEILLANCE IN NORTHERN ARIZONA

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INTRODUCTION

Coccidioides species are the etiological agent of the disease valley fever. Human disease ranges from asymptomatic to acute or chronic pneumonia and in severe cases dissemination. Arizona has the highest rate of cases reported each year. In moderately endemic regions such as Northern Arizona the risk of getting the disease is lower. However lack of awareness can increase the risk of delayed diagnosis and treatment. Which is known to increase the risk of severe pulmonary disease or dissemination to the central nervous system, bones and joints. To determine the impact of valley fever in Northern Arizona we investigated public health records, hospital data and the genetic composition of local clinical isolates. In addition we conducted a preliminary survey of soils for evidence of *Coccidioides*.

METHODS

The Arizona Department of Health database was queried by county. Patients charts were investigated from the regional hospital and random samples of fungal isolates from cases in Coconino County were sequenced. In addition a collection of 100 soils from Coconino and Mohave county were subjected to standard *Coccidioides* DNA extraction and qPCR amplification protocols.

RESULTS

In Northern Arizona the highest rate of cases occurred in Coconino and Navajo County whereas lower rates occurred in Apache, Yavapai and Mohave County with slight fluctuations each year. The regional hospital treated several cases of severe valley fever. In patients with health complications such as HIV, diabetes and cancer extrapulmonary dissemination often occurred. All of the isolates obtained from local cases clustered with the *Coccidioides* populations from either the Phoenix or Tucson area. In 100 soils, 6 from Coconino County and 12 Mohave County were positive through CDx assay.

CONCLUSION

While we detected evidence of *Coccidioides* spp. in Northern Arizona soils we consider the evidence preliminary. The isolates obtained from the regional medical center are genetically related the Southern Arizona *Coccidioides* population. Individuals living in moderate endemic regions of Arizona are risk of contracting valley fever. Severe cases of disseminated valley fever often occurred in patients with additional health complications. Our findings highlight the need for increased awareness among physicians, local health officials and the public in the region.

ANALYSIS OF COCCIDIOIDOMYCOSIS TEST DATA FROM A LARGE COMMERCIAL LABORATORY IN ARIZONA, 2013-2017

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INTRODUCTION

The Arizona Department of Health Services (ADHS) conducts laboratory-based surveillance for coccidioidomycosis. ADHS obtained data on positive and negative *Coccidioides* tests from a large commercial reference laboratory. We analyzed demographic characteristics as well as trends in laboratory tests and percent positivity over time.

METHODS

Data for all *Coccidioides* laboratory tests performed at a large commercial reference laboratory between January 2013 and January 2018 were obtained. Equivocal or indeterminate results were classified as negative. We assumed tests were performed on serum unless labeled as CSF in test code or test label. Titers of ≤1:2 from serum were treated as negative. For the patient-level analysis, we restricted the data to laboratory results associated with the earliest collection date.

RESULTS

There were 816,214 laboratory test results for the study period. After restricting the dataset to Arizona residents and tests with specimen collection dates during the study period (1/1/2013–12/31/2017), 754,925 test results for 248,012 patients remained. The number of patients tested ranged from 40,303 in 2014 to 54,235 in 2016. Patients were mostly female (range: 56–59%), and the mean age ranged from 50 to 54 years. A majority were residents of Maricopa County (range: 73–78%). The most frequent pattern of test results was negative EIA (67%) and negative EIA and negative complement fixation (12%). Among the subset of patients with EIA results (n=222,462), EIA IgM positive patients were younger than EIA IgM negative patients (mean age 46 vs. 52 years). However, EIA IgG positive patients were slightly older than EIA IgG negative patients (mean age 55 vs. 52 years). EIA IgG positive patients were more likely to be male than EIA IgG negative patients (52% vs. 42%); there was no difference in sex distribution by EIA IgM status. Trends in monthly proportion of positive EIA tests varied by antibody and had distinct seasonal patterns.

CONCLUSION

Our analysis demonstrated that demographic characteristics for patients tested at the commercial laboratory remained relatively consistent over time but noted interesting differences when examined across laboratory tests. More insight into healthcare seeking behaviors and provider decision-making regarding testing may explain some of these unexpected results.

COCCIDIOIDOMYCOSIS, ASPERGILLUS AND HISTOPLASMOSIS: CLINICAL AND EPIDEMIOLOGICAL CONTRASTS IN PATIENTS HOSPITALIZED AT THIRD LEVEL OF CARE IN MEXICO.

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Introduction: The three main fungal infections with pulmonary and systemic affection are caused by Coccidioidomycosis "**Cocc**", Aspergillosisi "**Asp**" and Histoplasmosis "**Hist**" these share some clinical, radiological and epidemiological characteristics that make timely treatment difficult due to the similarities with other respiratory diseases such as pulmonary tuberculosis
Objectives: Describe the clinical and epidemiological characteristics between "**Cocc**", "**Asp**" and "**Hist**" to help early diagnosis.
Methods: A retrospective study was carried out at the INER. Patients with a confirmatory diagnosis of **Cocc** "," **Asp** "and" **Hist** from 2007 to 2017 were included, the prevalence and lethality were calculated, a statistical analysis was performed and the groups of patients with these 3 pulmonary mycoses were compared, we used the U test of Mann-Whitney for continuous variables, and the Chi-square test and Fisher's exact test for categorical variables, SPSS was used, see 22, significance levels were considered with a P value <0.05, two tails.
Results: The overall prevalence increased from 7.72 to 10.82, and a decrease in the lethality from 9 to 6.3 per 1000 discharges. The main significant differences (P <0.5) were age, sex, days of stay and mortality, however, no differences were found between some risk factors, sex and comorbidities, **Conclusions:** It is suggested to make a differential diagnosis of "**Cocc** "," **Asp** "and" **Hist** in patients with a pulmonary pattern of miliary lesions, especially when the patient has an immunological deficiency with or without a history of risk for coccidioidomycosis, aspergillosis or histoplasmosis, and when they have an infectious respiratory disease of torpid evolution, and long-term hospital stay.

Frequencies of coccidioidomycosis and other fungal infections during 27 years in the National Institute of Respiratory Diseases "Ismael Cosío Villegas".

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INTRODUCTION: Mycoses are serious and potentially lethal diseases, especially those that are invasive and that have pulmonary disease, presenting nonspecific symptoms that make timely diagnosis difficult. In Mexico, the most common route of infection of fungal infections is through visits to areas that are endemic and / or related to work activity. The present work shows the incidence of the most frequent pulmonary fungal infections over 27 years.

MATERIAL AND METHODS: A retrospective study was conducted during the period 1992 to 2018, of the entire database of a total of 879 patients diagnosed with pulmonary fungal infections, the data was obtained with the support of the strategic planning department, organizational development and the Biostatistics area of the INER.

RESULTS: The analyzed data showed that the main fungal infections are: pneumonitis (37.54%), aspergillosis (20.47%), histoplasmosis (18.54%), coccidioidomycosis (12.62%) and nonspecific mycosis (5.23%). For this study candidiasis was not taken into account because the cases diagnosed were in patients with immunosuppression (HIV-AIDS) and presented as oral and non-pulmonary mycosis.

DISCUSSION: Mycotic infections are not the first diagnostic option in symptomatic patients with pulmonary disease, due to the similarity with other pathologies such as tuberculosis. In Mexico there are no epidemiological platforms where mycosis is reported, therefore, we consider that they are under-diagnosed and that statistics are needed to show incidences in Mexico.

CONCLUSIONS: In our institution, patients from a large part of the country with chronic lung diseases of various etiologies are concentrated, observing that mycosis plays an important role in this type of pathologies. For all the above, this work is of great interest because it provides accurate data about the mycotic infections diagnosed in patients with lung conditions for 27 years.

SELF-ORDERED TESTING FOR COCCIDIOIDOMYCOSIS IN ARIZONA

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INTRODUCTION

In 2016, a major commercial laboratory (Lab A) in Arizona began performing self-ordered enzyme immunoassay (EIA) tests, also known as direct access tests (DATs), for coccidioidomycosis. We interviewed patients who had a positive DAT to evaluate the patient's reasons for ordering the test and healthcare seeking before ordering the DAT and after receiving their results.

MATERIALS AND METHODS

Lab A provided de-identified and de-duplicated data to the Arizona Department of Health Services (ADHS) that included results for all DATs ordered from October 2016 through June 2018. The data were matched to ADHS surveillance data, which includes positive DATs already reported. A script and questionnaire were developed and used to interview Arizona residents who tested positive.

RESULTS

The data contained 1,934 records (IgM and IgG results for each test ordered), corresponding to 965 unique patient visits for DAT testing. Of these, 79 (8%) tested positive (IgM, IgG, or both) and 68 individuals could be identified in MEDSIS—of which, 17 (25%) had a positive test before their DAT. Of the 19 patients interviewed, 16 (84%) reported coccidioidomycosis symptoms, which began a median of 80 days before their positive DAT. Regarding reasons for testing, 11 (58%) said they weren't feeling well and thought they might have it, 8 (42%) said it was more convenient, 2 (11%) said their doctor would not test them, and 2 (11%) said it was cheaper than going to the doctor. Fourteen (74%) reported at least one healthcare visit for their symptoms prior to their DAT, and for those whose first positive coccidioidomycosis test was their DAT, 11 (58%) reported at least one healthcare visit prior. Overall, 15 (79%) followed up with a healthcare provider.

CONCLUSION

Direct access testing for coccidioidomycosis provides a new opportunity for patients to be diagnosed, and the utilization of DATs and reasons for testing should continue to be monitored.

COCCIDIOIDOMYCOSIS IN BAJA CALIFORNIA

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INTRODUCTION

The state of Baja California has been considered as an endemic area of coccidioidomycosis; however, there are few epidemiological data about the behavior of the disease. An eco-epidemiological study was designed to achieve the following objectives, a) to know: the species involved in six patients infected with Coccidioides, the infection frequency in general population, the number of disease cases in the state, and 2) to isolate Coccidioides spp. from the air of the region.

MATERIALS AND METHODS

Genotyping of patients' isolates. Two types of amplification were performed: 1) PCR and sequencing of Fisher's 621 microsatellite and 2) Umeyama PCR. Intradermal survey. Coccidioidin was applied in 86 patients. Number of cases. Three information sources from the Ministry of Health were consulted. Isolation. The air was sampled by gravimetric precipitation in Petri dishes.

RESULTS

By microsatellite 621 sequencing, all patients' strains were identified as C. immitis. We obtained 24 positive patients to IDRcoccidioidine from 86 applications. In the period 1989-2018 there were 182 cases of coccidioidomycosis in the state. Coccidioides spp. did not grow from the air.

CONCLUSION

Six cases of coccidioidomycosis in a period of just over a month, caused by the same species, implies an epidemic outbreak. The proportion of IDR+ (27%) shows a high prevalence of infection; on the contrary, new cases of coccidioidomycosis registered in 29 years are scarce and the isolation of the fungus should be attempted from other substrates.

SOURCES OF VALLEY FEVER INFORMATION REPORTED BY KERN COUNTY FARM WORKERS

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INTRODUCTION: As part of a KABB study on Valley Fever among seasonal farm workers in Kern County, data were collected to design an educational campaign among this population.

MATERIALS AND METHODS: Interviews assessed knowledge accuracy, sources of Valley Fever information, work history, migration patterns, health problems, and health information sources. Two migrant housing centers were accessed from June through October 2017 with the approval of the Kern County Housing Authority. Participant inclusion criteria were age >17 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.

RESULTS: 60 males and 59 females participated in the study. Ages ranged from 18 to 71 years, with a mean of 42 years. 105 (88.2%) participants reported being born in Mexico. 93.3% reported speaking Spanish at home. Reported sources of health information included: family, friends and co-workers (61.5%), healthcare providers (54.5%), print media (12.3%), internet (22.3%), market/pharmacy (15.4%), community/housing center presentations (13.8%), workplace (37.4%), radio (44.7%), and television (73%). 87 participants reported hearing of VF prior to the interview. 49.4% (n=43) of these participants either had a history of VF (n=7) or had a friend, relative or co-worker with a history of VF. The Total Knowledge Score (14 items) was mean=9.22, std dev = 0.50, (0-11). None of the bivariate correlation coefficients calculated for the overall knowledge score and several IVs were significant: Education (r=0.03); Income (r=0.02); Time in Kern County (r= -0.05); Time in outdoor agriculture (r= -0.07); Age (r= -0.06); Gender (r=0.04); Had VF or close relationship/acquaintance with VF history (r= 0.06).

CONCLUSIONS: Several participants knew someone with a history of Valley Fever, or had Valley Fever themselves. However many inaccuracies regarding acquisition, symptoms and prevention of Valley Fever were identified, suggesting that little accurate information was being accessed by this population. No IVs were identified in this analysis as being associated with Valley Fever knowledge. Results indicate a need for Valley Fever education targeting this high-risk population using peer education, healthcare providers, radio and television.

Coccidioidomycosis outcomes among hospitalized pregnant women – California, 2000 – 2016

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INTRODUCTION: Coccidioidomycosis in pregnancy has been associated with severe, disseminated disease; however, published data are largely limited to case reports with minimal information regarding neonatal outcomes. Utilizing California administrative hospitalization and birth registry data, we describe outcomes among pregnant and post-partum women hospitalized with coccidioidomycosis.

METHODS: We extracted records from 2000-2016 for women of childbearing age (14-45 years) hospitalized in California with coccidioidomycosis discharge diagnoses codes; and matched records to the birth registry to identify women who were pregnant or post-partum (within 30 days of childbirth) during their hospitalization. We compared demographics, risk factors, and outcomes by chi-square and t-test (significance, $p<0.05$) between pregnant and non-pregnant women hospitalized with coccidioidomycosis; and described birth outcomes of newborns of pregnant women hospitalized with coccidioidomycosis.

RESULTS: We identified 2,442 hospitalized women with a coccidioidomycosis diagnosis. Of these, 183 (7.5%) were pregnant or post-partum during ≥1 coccidioidomycosis hospitalization, 7 whom died; 184 newborns (one set of twins) were identified, including one who died. Pregnant or post-partum women (n=183) were more likely to be Hispanic (59.0% vs. 41.0%, p=0.0001), younger (median age: 27 vs. 34 years, $p<0.0001$), or without comorbidities (61.8% vs. 36.6%, $p<0.0001$) than non-pregnant women (n=2,259) hospitalized with coccidioidomycosis. The proportion of in-hospital deaths was similar (3.8% vs. 3.9%, p=0.92) between the groups. Among 183 pregnant or post-partum women, 140 (76.5%) were first hospitalized for coccidioidomycosis in the third trimester and four (2.2%) post-partum. Pregnant and post-partum women were more likely to have disseminated coccidioidomycosis (26.8% vs. 14.6%, $p<0.0001$) than non-pregnant women. Twelve (7.1%) of the 169 newborns with available birth gestational age were born <34 weeks gestational age, and 36 (19.6%) of 184 newborns had a birth weight <2500g.

CONCLUSIONS: Although limited by administrative hospital data, this study is the largest cohort of pregnant women with coccidioidomycosis to date. Our analysis supports that pregnant and post-partum women are more likely to develop disseminated coccidioidomycosis than non-pregnant women. This highlights the need for clinicians caring for pregnant women, including obstetrician-gynecologists, in endemic areas to be aware of coccidioidomycosis risks among pregnant women.

COCCIDIOIDOMYCOSIS OUTBREAK AMONG WILDLIFE BIOLOGISTS WORKING AT A SOLAR FARM — SAN BENITO COUNTY, CALIFORNIA, 2016–2018

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Background: In October 2017, the San Benito County Public Health Services (SBCPHS) identified 9 coccidioidomycosis cases among wildlife biologists who worked at a solar farm construction site. Endangered animal species inhabited borrows located within the construction site, which required excavation and relocation to minimize environmental impact. The California Department of Public Health and SBCPHS initiated an investigation to determine outbreak magnitude, identify risk factors, and recommend control measures.

Methods: We matched employee rosters to state surveillance data to identify workers with coccidioidomycosis. We interviewed workers and reviewed medical records to confirm ≥1 respiratory and ≥1 systemic symptom. Cases were defined as symptom onset ≥1 week after starting and <1 month after finishing work among solar farm workers. Confirmed cases required a positive *Coccidioides* immunoglobulin M or immunoglobulin G serology; clinical cases lacked laboratory confirmation, but required report of symptom duration of ≥3 weeks.

Results: Employee rosters were obtained from 16/24 (67%) contractor companies, including all 9 environmental companies. During May 2016–November 2018, 18 cases were identified (16 confirmed and 2 clinical) among 695 workers (attack rate, 2.6%), including 13 (72%) wildlife biologists, 4 (22%) laborers, and 1 (6%) engineer. Among 10 patients available for interview, 6 sought emergency department care, 4 were hospitalized (median length of stay: 4.5 days), and 9 missed work (median: 8 days) because of illness. All reported manually digging; all used respirators, 7 of whom reported always wearing respirators. Six patients reported soil was never or rarely wetted before digging; 9 reported receiving coccidioidomycosis safety training from employers.

Conclusions: Despite receiving coccidioidomycosis training and using respirators, workers, particularly wildlife biologists, developed coccidioidomycosis, likely because of exposure while manually digging. Because wildlife biologists will continue working on projects in endemic areas, improved education and training for prevention of coccidioidomycosis among this population is needed.

COCCIDIOIDOMYCOSIS OUTBREAKS AMONG INMATE WILDLAND FIREFIGHTERS IN CALIFORNIA

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INTRODUCTION: Wildland firefighting tasks that involve disturbing dirt in areas endemic for *Coccidioides spp.* likely pose a risk for coccidioidomycosis (cocci), but published reports have been limited to anecdotal findings.

MATERIALS AND METHODS: We compiled information on cocci cases among juvenile wards in work camps and among California Department of Corrections and Rehabilitation (CDCR) adult inmate wildland firefighters. We reviewed the literature, historical memos and reports, and California Correctional Health Care Services cocci case surveillance, outbreak notifications, and consultation notes for the CDCR cases. For the most recent outbreak among CDCR inmate firefighters, we collaborated with the California Department of Public Health (CDPH) on a survey to identify additional cases and specific work-related exposures.

RESULTS: In 1959 and 1965, 14 juveniles and three men at Scudder probation work camp (Los Angeles County) developed cocci. Assignments included cutting brush, shoveling dirt, and building fire breaks. We identified two cocci clusters (25 cases) among California Youth Authority wards in work camps (2000–2006). In 2000, 21 of 22 lab-confirmed case-patients worked behind a bulldozer breaking fire line in McKittrich (Kern County). We identified five cocci clusters (23 cases) among CDCR adult inmate wildland firefighters (2010–2017). In 2010, two inmate firefighters hospitalized with cocci pneumonia reported exposure to dust while working behind a chain saw used to cut up rats nests while training at Eagle Ranch. In 2011, there were three clusters involving 11 inmate firefighters with cocci pneumonia (four hospitalized); three fought a fire near McKittrick, two fought a fire in Coalinga, and six fought fires near Bakersfield. In 2017, ten inmates deployed to a fire near Coalinga developed cocci; two were hospitalized: one with cocci meningitis and another with respiratory failure. The CDPH survey found case-patients were more likely to report cutting fire line with a McLeod hand tool, tossing dirt in the air, and frequently being in a dust cloud.

CONCLUSION: We found documented repeated cocci outbreaks among inmate wildland firefighters working on hand crews dating back to 1959. Cocci should be considered an occupational risk for firefighter hand crews, which in California, include inmates and their civilian supervisors.

Regional Analysis of Coccidioidomycosis Cases, California, 2000 – 2017

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INTRODUCTION: Coccidioidomycosis incidence rates have increased substantially in California since 2000; the highest annual incidence ever reported in California to date was in 2017. Given recent reports of coccidioidomycosis outbreaks in areas thought to be less endemic, we analyzed surveillance data by region for the first time to better understand geographic trends in coccidioidomycosis.

METHODS: Using California coccidioidomycosis surveillance data from 2000–2017, we calculated age-adjusted incidence rates per 100,000 population and stratified by region: central valley (CV), central coast (CC), northern San Joaquin Valley (NSJV), southern coast (SC), southern inland (SI), southern bay area (SBA), northern and eastern California (NEC). We calculated relative risk (RR) of coccidioidomycosis by year (continuous), sex, age group, race-ethnicity, and region using multivariable negative binomial regression (significance, p-value<0.05) to assess trends and demographic risk. We calculated rate ratios comparing 2000 to 2017 and 2014 to 2017 to describe overall and regional changes.

RESULTS: From 2000–2017, 57,642 coccidioidomycosis cases (median annual incidence 7.8/100,000) were reported in California with the highest median annual incidence in the CV (86.7) and CC (9.4) compared with other regions (incidence range 0.5–5.4). From 2000–2017, incidence increased significantly statewide and within each region; with a 7.6-fold statewide increase and higher rate ratios in the NSJV (12.9) and SC (9.0) than other regions (range, 3.9–7.6). Comparing 2014 to 2017, rates increased 3.2-fold statewide with the highest rate ratio in the CC (8.8) than in other regions (range, 2.4–3.1). RR of coccidioidomycosis was significantly higher in males than females (RR 2.22), black than whites (RR 2.14) and with older age groups (RR 3.45, 20-39 years; RR 5.86, 40-59 years; RR 5.93, ≥60 years) compared with individuals <20 years.

CONCLUSIONS: Although coccidioidomycosis incidence has consistently been the highest in the CV region of California, substantial increases are occurring outside of that region which could indicate increased levels of endemicity; changes in work or recreation travel patterns; testing and reporting practices; and/or changes in population susceptibility. Both statewide and regionally, males, blacks, and adults are at increased risk for coccidioidomycosis.

BASIC SCIENCE

ID OF COCCIDIOIDES SPECIES BY HIGH RESOLUTION MELTING ANALYSIS

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INTRODUCTION

In spite of the recent advances in genotyping techniques, genus *Coccidioides* is still considered a biological conundrum. The uncertain information about its physiology, pathogenic mechanisms, epidemiology and geographic distribution leads to the idea of implementing a simple yet robust method to identify species. High-resolution melting (HRM) analysis is known to be a fast, low-cost alternative for other genotyping methods. In this work, HRM analysis was standardized and performed to identify both *C. immitis* and *C. posadasii* from culture isolates from various clinical specimens of inpatients of Mexico´s National Institute of Respiratory Diseases (INER) dated from 1998 to 2018.

METHODS

A classic approach using morphologic characteristics was used to identify the genus from various pulmonary secretion samples. DNA Isolation from Plant: DNeasy Plant Mini Kit (QIAGEN) kit was used for DNA extraction from culture isolates. A simple agarose gel quality check assay was performed to verify the integrity of nucleic acid material. Three primer pairs were designed following the 621 microsatellite-containing locus sequence; one out of these pairs yielded best quality results in a first Real-Time PCR assay, thus it was used in the high-resolution melt curve analysis. RT-PCR reaction was optimized using KAPA SYBR® FAST Universal 2X qPCR Master Mix (ROCHE). Data obtained from the melt curve analysis using Rotor-Gene® ScreenClust HRM® Software (QIAGEN) was compared to Sanger sequencing data, which was performed in order to assign species and prove the effectiveness of the technique.

RESULTS

Melting temperature values showed a mean difference of 0.5°C between both, *C. immitis* and *C. posadasii* isolates. Resulting in two well delimitated populations. Five out of 29 samples, identified as *C. immitis* by Sanger sequencing, produced a mean Tm of 79.5°C, whilst twenty-four samples, with a mean Tm value of 79.0°C were identified as *C. posadasii.*

CONCLUSION

High-resolution melting analysis has a forthright potential to become the method of choice to identify species of *Coccidioides* mainly for epidemiologic and biogeographic research purposes.

CARBO-LOADING IN FUNGAL LUNG PATHOGENS: A QUANTITATIVE ANALYSIS OF CAZYME ABUNDANCE AND RESULTING GLYCAN POPULATIONS

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INTRODUCTION: *Coccidioides spp.* are important and common pneumonia-causing pathogens of the American southwest, but little is known about their glycobiology or how their protein glycosylations differ from other pneumonia-causing fungi. There is mounting preliminary evidence to suggest genus or even species-specific glycosylations in the fungal kingdom due to unique carbohydrate active enzyme (CAZyme) presence in different fungal genomes.[1,2] If *Coccidioides spp.*-specific CAZyme profiles or glycans can be identified, it is possible to exploit these differences to develop more specific diagnostic approaches and therapeutics.

MATERIALS AND METHODS: We performed laser capture microdissection (LCM) of 3 uninfected patient controls, 3 *Coccidioides spp., 3 Histoplasma spp., 3 Aspergillus spp.,* and *3 Cryptococcus spp*. – infected lung tissues, for N-glycomics using mass spectrometry. Glycomics of LCM tissue was performed using a "Dot Blot" N-glycan deglycosylation protocol prior to LC/MS. Mycelial and spherule fungal cultures of *Coccidioides posadasii* strain Silveira were prepared in 6 different media and extracted by GeLC-MS/MS for proteomics and glycomics. Protein abundance was performed using a label-free protein quantification.

RESULTS: Many CAZyme classes and families encoded in the 7 published sequenced genomes of *Coccidioides spp.* are expressed *in vitro* (70.8%) and *in vivo (35.9%)*, and suggest possible genus- and species-specific CAZyme profiles. CAZyme protein abundances of certain key enzymes were significantly different between mycelial and spherule forms and dependent on culture media used. The majority (~75%) of N-glycans in all fungal-infected and non-infected lung tissues were unknown glycan structures. However, mass spectrometry revealed 4 *Coccidioides spp*.-specific glycan structures from infected lung tissues identified in all *Coccidioides spp.*-infected lung tissues and *in vitro C. posadasii* lysates, but not in normal lungs or lungs infected with other fungi. These *Coccidioides spp*.-specific glycans have motifs not previously reported in the literature for fungi.

CONCLUSION: We provide genomic evidence that *Coccidioides spp*. CAZyme profiles differ from other common pneumonia-causing fungi and show protein abundances of *Coccidioides posadasii* strain Silveira CAZymes differ *in vivo* and *in vitro,* as well as varying by media formulation and growth phase. The key CAZymes upregulated in the spherule phase could be interesting therapeutic targets.

ELUCIDATING MOLECULAR DETERMINANTS OF *COCCIDIOIDES* (VALLEY FEVER) INFECTIONS IN THE SOUTHWESTERN UNITED STATES USING GENOME WIDE ASSOCIATION STUDIES

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INTRODUCTION: Valley Fever is caused by the fungal pathogen *Coccidioides,* which infects, colonizes, and can kill healthy humans when they inhale fungal spores from desert soils. In the endemic areas of the US, namely Arizona and Southern California, infection rates have increased 8-fold in the last decade and doubling annually in the last three years. Although research is ongoing, there are currently no vaccines and for the deadliest infections, current antifungal drug therapies are often of minimal efficacy. The urgent need in the field is for large-scale mapping of genotype to phenotype in *Coccidioides*, to accelerate the discovery of genes that can be targeted for development of novel drugs and/or vaccines.

MATERIALS AND METHODS: The purpose of this study is to identify genes that underlie virulence phenotypes such as infectious spore (spherule) production, by profiling population genomic and phenotypic diversity in clinical *Coccidioides* isolates. We are conducting a series of natural-variation-based screens in *Coccidioides* isolates from a panmictic population using genome variant scans to find evidence of natural selection in spherulation and other virulence related traits across the population.

RESULTS & CONCLUSION: We have found obtained and sequenced ~100 individuals of *Coccidioides posadasii* from Pima County Arizona. We have confirmed using variant profiling, phylogenomics and metrics of population diversity and selection that GWAS is likely to identify novel genetic determinants of infections and potential targets for novel therapeutics. Analyzing population level genomic diversity in a genome wide association study (GWAS) framework is a relatively straight forward screening approach, and which we have adapted to understanding traits relevant for virulence in *Coccidioides.* Adaption of GWAS to *Coccidioides,* population structure and diversity, and preliminary GWAS results will be discussed.

ACCURATE COCCIDIOIDOMYCOSIS DETECTION USING TARGETED PLASMA AND URINE METABOLIC PROFILING

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INTRODUCTION: Coccidioidomycosis, also known as valley fever (VF), is a potentially lethal fungal infection that results in more than 200 deaths per year in the United States. Despite the important role of metabolic processes in the molecular pathogenesis of VF, robust metabolic markers to enable effective screening, rapid diagnosis, accurate surveillance, and therapeutic monitoring of VF are still lacking.

MATERIALS AND METHODS: In this study, we present a targeted liquid chromatography-tandem mass spectrometry (LC-MS/MS)-based metabolic profiling approach for identifying metabolic marker candidates that could enable rapid, highly sensitive and specific VF detection. Using this targeted approach, 207 plasma metabolites and 231 urinary metabolites from numerous metabolic pathways of potential biological significance were reliably detected and monitored in 147 samples taken from two groups of subjects (48 VF patients and 99 non-VF controls).

RESULTS: Our univariate significance testing and multivariate model estimation informed the construction of a 3-metabolite panel of potential plasma biomarkers and a 9-metabolite panel of potential urinary biomarkers. Receiver operating characteristic (ROC) curves generated based on orthogonal partial least squares-discriminant analysis (OPLS-DA) models showed excellent classification performance (99.5%), with 94.4% sensitivity and 97.6% specificity for plasma metabolites. Urine metabolites were less accurate (92.9%), demonstrating 89.7% sensitivity and 88.1% specificity. Enrichment, pathway, and network analyses revealed significant disturbances in glycine and serine metabolism in both plasma and urine samples.

CONCLUSION: To the best of our knowledge, this is the first study investigating novel VF metabolite markers for accurate diagnosis within 24 hrs. The results expand basic knowledge of the metabolome related to VF and potentially reveal pathways or markers that could be targeted therapeutically. This study also provides a promising basis for the development of larger multi-site projects to validate our findings across population groups and further advance the development of better clinical care for VF patients.

A CANINE TARGET SPECIES CHALLENGE MODEL TO EVALUATE EFFICACY OF A COCCIDIOIDOMYCOSIS VACCINE

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Introduction: The preferred efficacy design for licensing a vaccine for animal use (United States Department of Agriculture (USDA), Center for Veterinary Biologics) is a prospective, placebo-controlled, randomized, and double-blinded vaccination-challenge trial. In such studies, each subject receives the same exposure to the virulent pathogen by active challenge. To test a Δcps1, live avirulent canine coccidioidomycosis vaccine, a challenge inhalation disease model was developed in beagle dogs.

Methods: 6-month old male beagle dogs were socially housed according to PHS standards. All procedures were approved by the Institutional Animal Care and Use Committee for Colorado State University and were performed at ABSL3. Dogs were infected by nebulization with low, medium or high counts of arthroconidia of *Coccidioides posadasii*, strain Silveira, delivered via endotracheal tube under injectable anesthesia. Daily observations plus thoracic radiographs, CBC, and serum chemistries and body weights were obtained at 2- or 3-week intervals and dogs were humanely euthanized 8 weeks post-infection, or earlier if necessary. Approximately 1 gram lung specimens from each lobe were cultured for fungal burden. Fixed lung specimens were prepared for histological examination. Serum was tested for antibodies.

Results: Nebulization failed in one dog for technical reasons. Among the other 10 dogs, 5 required early removal at 33- or 48-days following challenge. Elevated globulin, decreased albumin, decreased A/G ratio, monocytosis and weight loss were present in all infected dogs. Significant radiographic lesions were more diffuse and extensive at the high challenges and, similarly, gross, histopathological, and radiographic scores were more extreme in these subjects. The middle doses had the most consistent scoring and clinical features, including some early removal. The lowest dose was least consistent with lower clinical scores overall. All dogs developed antibodies.

Conclusions: Nebulized aerosol delivery of spores reproducibly produced significant coccidioidomycosis in 10 of 11 dogs. Overall the challenge model, demonstrated consistent characteristic findings sufficient to assess vaccine efficacy in dogs during an 8-week period post challenge without producing a potentially overwhelming infection. The aerosol nebulization of arthroconidia in beagle dogs should provide a vaccination-challenge experimental design in line with Chapter 9 Code of Federal Regulations, parts 102.5 and 104.5.

IMMUNE CELL DIFFERENTIATION IN RESPONSE TO COCCIDIOIDES

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INTRODUCTION: *Coccidioides* infection occurs when arthroconidia is inhaled into the lung and undergoes morphological changes from soil (arthroconidia) to host form (spherule). Effective *Coccidioides* clearance requires monocyte migration into the site of infection and subsequent differentiation. Macrophages and neutrophils mediate fungal clearance via phagocytosis and effector cytokine secretion. Little is known about the dynamics and interactions between immune cells and *Coccidioides* at the start of infection. Flow cytometry is a powerful tool that can elucidate protein expression and, with traditional function assays, can be used to characterize *Coccidioides* impact on immune cells, such has been used for *Histoplasma* and intracellular bacterial studies. This allows for examination of *Coccidoides* influence on recruited immune cell differentiation and fungal clearance efficacy.

MATERIALS AND METHODS: *Coccidioides posadasii* (NR-166), an avirulent lab strain, was cultured and processed to obtain arthroconidia suspension for mouse infections and *in vitro* experiments. Human monocyte U937 and mouse macrophage RAW 264.7 cell lines were used in differentiation and phagocytosis assays. Cells were stimulated and infected, then harvested and stained for differentiation markers. Flow cytometry, imaging and microscopy were used to assessed their function.

RESULTS: We have defined a method for evaluating fungal infection by identifying membrane bound versus internalized *Coccidioides* by flow cytometry. Our data demonstrate that *Coccidioides* alone is insufficient to induce monocyte differentiation into macrophages. However, the shift towards macrophages, following stimulation, is enhanced in the presence of *Coccidioides*. Monocytes cannot phagocytose *Coccidioides* effectively compared to macrophages and differences in phagocytosis were observed within distinct macrophage subtypes. *In vivo* infections with increasing *Coccidioides* doses demonstrated distinct kinetics of immune infiltrate and localized lung activation.

CONCLUSION: We have adapted a protocol for measuring macrophage phagocytosis of *Coccidioides* by flow cytometry. Our data suggest that *Coccidioides* enhances monocyte differentiation but only in the presence of pro-inflammatory signals and/or damage signals. Monocytes are incapable of engulfing or clearing *Coccidioides* as effectively as macrophage, indicating strong pro-inflammatory responses are necessary for effective clearance. Ongoing in vivo experiments will assess monocyte differentiation patterns and early immune interaction within the lung microenvironment following infection and the impact of these signals on adaptive immunity.

IDENTIFYING VOLATILE BIOMARKERS FOR A VALLEY FEVER BREATH TEST

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INTRODUCTION: The current diagnostics for Valley fever are severely lacking due to poor sensitivity (via serology) and invasiveness (via biopsy), leading to delayed diagnosis, inappropriate treatment with antibiotics, lost productivity, and increased medical costs. There is a critical need for sensitive and non-invasive diagnostics for detecting and identifying Valley fever lung infections. Our long-term goal is to substantially shorten the time-to-diagnosis for Valley fever through the development of sensitive and specific breath-based diagnostics for coccidioidomycosis lung infections. In the near-term, we are working toward identifying volatile biomarkers of *Coccidioides posadasii* and *C. immitis* infections via metabolomics analyses of *in vitro* cultures, murine model lung infections, and lung specimens from humans with Valley fever. Herein we present recent data on the volatile profiles of *C. posadasii* and *C. immitis* grown *in vitro* as spherules and as mycelia.

METHODS: Six strains of *C. posadasii* (three AZ and three TX/MEX/SA population strains) and six strains of *C. immitis* (three SJV and three SDMX strains) were cultured in triplicate for 96 h in Converse media at 39ºC in 5% CO_2 and 1% O_2 to induce spherule formation, and normoxia at 28ºC for mycelial formation, yielding 72 cultures. The spent media were filter sterilized for volatile metabolomics analyses by headspace solid phase microextraction (HS-SPME) and two dimensional gas chromatography could with time-of-flight mass spectrometry (GCxGC-TOFMS). The metabolomes of each strain under each condition were compared using univariate and multivariate analyses.

RESULTS: We have identified volatile metabolites that are commonly produced by both species of *Coccidioides* during mycelial growth, and during spherule formation. Additionally, we identified compounds that are unique to each species. The next steps of this work will be to collect the volatile metabolites from lung lavage specimens of uninfected and infected mice to identify which of the *in vitro* volatile compounds translate to *in vivo* infections.

CONCLUSIONS: *C. posadasii* and *C. immitis* produce volatile metabolites that may be useful in the development of a breath-based diagnostic for Valley fever lung infections.

VETERINARY

CLINICAL FEATURES OF CATS DIAGNOSED WITH COCCIDIOIDOMYCOSIS IN ARIZONA, 2004-2018

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INTRODUCTION

Little published information exists about coccidioidomycosis in cats. The goal of this study was to describe the presentation, diagnosis, and outcome of cats diagnosed with coccidioidomycosis in Arizona.

MATERIALS AND METHODS

A retrospective review of records was performed at both primary and tertiary care veterinary practices in Tucson and Phoenix, AZ. Data collected included the signalment, clinical signs, physical exam findings, diagnostic test results, treatment, and outcome. Descriptive analysis of data was performed.

RESULTS

Fifty-one feline cases were identified from six veterinary hospitals. Cats presented with clinical signs and laboratory abnormalities similar to what has been seen in dogs, including respiratory illness (20/51), neutrophilia (24/31), monocytosis (17/31), and hyperglobulinemia (16/30). However, cats at diagnosis were typically significantly ill, with 31/51 having disseminated infection, most commonly to the skin (n=22). Additionally, 43/44 cats that had serum antibody tests performed were positive, and median titer at diagnosis was 1:32 (range 1:4 - ≥ 1:256). Serum antibody titers reduced significantly ($P \leq 0.001$) in cats that responded to treatment compared with cats that did not clinically improve. 40/46 cats that were treated with oral fluconazole responded and did not require additional therapy. Fourteen cats developed recurrent disease and all but 1 had antifungal therapy successfully reinstituted.

CONCLUSION

In cats, coccidioidomycosis is most often disseminated at the time of diagnosis, possibly due to delays in presentation for care and recognition of the infection. Suspicion of disease, serum chemistries, blood cell counts, presence of antibody, and imaging aid in diagnosis of coccidioidomycosis in cats. Serum antibody reduction during treatment frequently correlated with an adequate response to medication. Despite the high rate of disseminated disease seen in the study population, most cats were successfully treated to clinical remission. Consideration of coccidioidomycosis as a cause of illness will lead to earlier diagnosis and potentially better treatment outcomes in cats.

EVALUATION OF A COMMERCIALLY AVAILABLE, POINT-OF-CARE *COCCIDIOIDES* ANTIBODY LATERAL FLOW ASSAY TO AID IN RAPID DIAGNOSIS OF COCCIDIOIDOMYCOSIS IN DOGS.

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Introduction:

Coccidioidomycosis in dogs can range from mild respiratory disease or vague, chronic malaise to acute, severe life-threatening illness. The diagnosis of coccidioidomycosis in dogs is based on clinical presentation, serology, and spherule identification if possible. Spherule identification is not typical because of low numbers of organisms in specimens, and the invasive nature of sampling tissues and lungs. Conventional serological assays require samples to be submitted to a reference laboratory and results take several days to one week. The sōna *Coccidioides* Antibody Lateral Flow Assay(LFA) (IMMY Diagnostics) is a rapid, bench-side test used for detection of *Coccidioides* antibodies. It is available and FDA-cleared for use in humans, but has not been evaluated in dogs.We compared the LFA to conventional agar gel immunodiffusion (AGID) serology for rapid screening of dogs in a critical care setting.

Materials and Methods:

Serum was collected from canine patients who were suspected to have coccidioidomycosis. Samples were screened by the LFA and submitted to a commercial reference laboratory for AGID screen and titer. The sōna *Coccidioides* Ab LFA test was performed on all serum samples by one technician who was blinded to the outcome of the case. The results of the AGID and LFA were compared by agreement analysis and the kappa coefficient was determined.

Results:

Of 56 serum samples analyzed, 30 were positive and 26 were negative on the sōna *Coccidioides* Ab LFA. The overall percentage agreement plus 95% CI was 87.5% (78.84, 96.16). Positive agreement was 89.7% (81.74, 97.66) and negative percent agreement was 85.2% (75.9, 94.5). The kappa coefficient to assess agreement was 0.749, 95% CI (0.576, 0.923). This is interpreted as good agreement between the tests (>70%).

Conclusion:

The sōna *Coccidioides* Ab LFA provided rapid, point-of-care results with a high level of agreement to standard AGID serology in dogs clinically suspected to have coccidioidomycosis.

CLINICAL

Tolerability of long-term fluconazole therapy

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BACKGROUND:

Fluconazole is a commonly prescribed first-generation triazole antifungal. Although the toxicity profile of fluconazole has been evaluated in clinical trials, there are scant data regarding its tolerability with long-term therapy. Treatment guidelines for coccidioidomycosis recommend fluconazole therapy and severe or disseminated infections can require lifelong treatment.

OBJECTIVES:

To assess the prevalence of long-term fluconazole adverse effects, their consequences for antifungal therapy, time to adverse effects and the association between dosing regimen or fluconazole serum level and adverse effect status.

METHODS:

We conducted a single-centre, retrospective study of adult patients (≥18 years) with proven or probable coccidioidomycosis receiving long-term fluconazole therapy for an intended duration of ≥28 days.

RESULTS:

Out of 124 patients included, 64 (51.6%) experienced adverse effects. The most common adverse effects were xerosis (16.9%), alopecia (16.1%) and fatigue (11.3%). Of the 64 patients experiencing adverse effects, 42 (65.6%) required a therapeutic intervention such as dose reduction, discontinuation or switch to a new antifungal. Patients experiencing adverse effects were prescribed higher total daily fluconazole doses (6.7 versus 5.7 mg/kg; $P < 0.01$). The median therapeutic drug levels did not differ significantly between patients who experienced adverse effects and those who did not (36.1 versus 28.1 mg/L; $P = 0.35$).

CONCLUSIONS:

A significant number of patients receiving long-term fluconazole therapy for coccidioidomycosis experienced adverse effects. Of these, around two-thirds required a therapeutic change. We believe these findings are representative of the adverse effect profile of long-term fluconazole therapy as it is used in clinical practice for coccidioidomycosis as opposed to use in clinical trials.

DELAYS IN COCCIDIOIDOMYCOSIS DIAGNOSIS AND ASSOCIATED HEALTHCARE UTILIZATION IN TUCSON, ARIZONA

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Coccidioidomycosis (Valley fever) is a fungal infection endemic to the southwestern United States and Mexico. When infection results in illness, it is typically a respiratory syndrome, and, without specific laboratory confirmation, cannot be distinguished from other causes of community-acquired pneumonia (CAP). Here we report a retrospective study within Tucson, to determine the delay between when patients first seek medical care and receive a laboratory-confirmed diagnosis of coccidioidomycosis. We also analyzed healthcare costs, efforts, and antibacterial drug use during that period.

A total of 815 charts were reviewed via EMR and 539 (66%) were excluded. Exclusions were for coccidioidomycosis prior to the study period (57%), mistaken coding (11%), age < 18 years (10%) and diagnosis not confirmed (22%). Of the remaining 276 cases, 126 (46%) were female, average age was 55. The distribution by disease category was acute symptomatic pulmonary (63%), chronic pulmonary (8%), asymptomatic pulmonary nodule (17%), and disseminated infection (12%). Overall, there was a median delay of 23 days (95% CI [17,34]) and approximately 43% of patients (95% CI [38,50]) had a delay of at least one month.

Of the 276 patients, 30 (11%) had their coccidioidal diagnosis established with tests ordered at the time of presentation (zero-day delay) and 12 of these were diagnosed during a hospital admission. Since the initial hospitalization was not required for diagnosis, we excluded their Valley fever-associated costs from the total of this group. For the remaining 264 patients, Valley fever-associated costs accounted for $594,847 (82.8%) of the $718,401 total. Overall, Valley fever-related costs for patients with a delay in diagnosis were significantly greater (p=0.0004) than for the 18 patients with no delay.

A total of 1103 orders for antibacterial drugs were submitted prior to diagnosis of coccidioidomycosis. Vancomycin and Daptomycin represented 22% of the antibiotics used.

Our results suggest that earlier diagnosis will lower costs, and provide secondary benefits including patient reassurance, decreased antibiotic use and improved antibiotic stewardship. This study reinforces the ongoing challenge to increase healthcare provider awareness of Valley fever, even in endemic areas, and the urgent need to improve the ease, rapidity and reliability of coccidioidomycosis testing.

INFORMATIC PROFILE OF PRIMARY CARE PRACTIONERS' TESTING AND MANAGING PATIENTS WITH COCCIDIOIDOMYCOSIS (CM)

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Introduction:
At least 43% of patients in our health care system with CM experience a diagnostic delay of > 1 month. We have therefore initiated a training program for general practitioners at 39 Arizona clinics, and developed informatic metrics of clinicians' practice patterns for diagnosis and management of new CM.

Methods:
The clinics use the same electronic medical record (Cerner), and data for 2017-18 is from the enterprise data warehouse. Only coccidioidal serologic tests (CSTs) ordered by patients' primary clinicians (physicians, NPs) were included. Multiple results for same patients were excluded within each year. Positivity percentages of CSTs were calculated from a single laboratory which furnished 78% of all CSTs. Newly assigned CM ICD10 codes (B38.*) were considered new infections if associated 60 days before or 30 days after a positive CST. We tabulated levofloxacin, azithromycin, cefdinir, doxycycline or amoxicillin-clavulanate prescriptions for the 2 months before and total referrals to pulmonary or ID consultants after diagnosis.

Results:
For 2017-18, 309 clinicians ordered one or more CSTs for 4,099 out of 282,449 total patients (1.7%) in primary care clinics. EIA accounted for 91% of CSTs. In 2018, no tests were ordered by 29.1% of clinicians, 1 by 19% of clinicians, 2 by 10.0%, 3-10 by 23.4%, and 11-96 by 20.6%. CST positivities were 0% for 59.0% of clinicians, 1.0-10% for 11.7%, 11-20% for 16.8%, and 21-67% for 10.6%. Test number ordered and test positivity were unrelated. Of 157 patients with new CM in 2017-18, 45.9% received 199 antibacterial prescriptions (2.8 prescriptions/patient), and 45.9% were referred for specialty care.

Conclusions/Discussion:
In our health care system, over half of clinicians tested 2 patients or fewer for CM annually, but some tested many more. Regardless of testing frequency, positivity ranged from 0% to 67%. Understanding this variability in diagnostic performance among clinicians could lead to a more precise understanding of who might benefit from CSTs. Our metrics confirm that multiple antibacterial prescriptions are commonly employed prior to accurate diagnosis and show that nearly half or patient management plans included subspecialty referral. These findings provide benchmarks for future evaluation of our new training program.

POSACONAZOLE-INDUCED APPARENT MINERALOCORTICOID EXCESS

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INTRODUCTION

Posaconazole is a triazole that resembles itraconazole, which has been associated with secondary hypertension and hypokalemia. There have been case reports of posaconazole-induced apparent mineralocorticoid excess (AME). However, its occurrence, association with serum posaconazole drug level, and predisposing factors need further investigation.

MATERIALS AND METHODS

In this single-center cross-sectional study, we examined patients on posaconazole who had laboratory evaluation for concerns for AME under a quality improvement initiative. We examined the occurrence of AME and evaluated differences in serum posaconazole drug level and clinical characteristics between those with and without AME. We diagnosed patients with AME if they had elevated serum 11-deoxycortisol, undetectable serum aldosterone, and low to low-normal renin activity. As part of the quality improvement initiative, patients diagnosed with AME had their posaconazole either dose-reduced, discontinued, or switched to an alternative antifungal. We instructed them to have their laboratory studies re-drawn after intervention to assess for improvement or resolution of their AME.

RESULTS

We examined 34 patients on posaconazole who had laboratory evaluation for concerns for AME; 19 were men (55.9%) with a median age of 56 years. 21 (61.8%) were on posaconazole for fungal prophylaxis in the setting of immunosuppression as opposed to active treatment for a fungal infection. 14 (41.2%) were diagnosed with AME. Patients with AME had a higher serum posaconazole level (ug/mL) than those without (2.8 vs. 1.9, P=0.02). These patients had a significant increase in mean arterial pressure (mmHg) (8.7 vs. -1.3, P=0.04) and a significant decrease in their potassium level (mEq) (-0.4 vs. 0.2, P=0.003) than those without AME. There were no significant differences in age, sex, ethnicity, milligram per kilogram dosing, or serum bicarbonate level.

CONCLUSION

Posaconazole-induced AME occurrence may be around 40%, more frequently than previously thought. AME was associated with a higher serum posaconazole level. Patient with the laboratory diagnosis of AME exhibited increased in blood pressure and decreased in serum potassium level, consistent with the clinical syndrome of AME. Clinicians should be aware of this adverse effect of posaconazole and consider interventions. We are pending follow-up data of patients with AME that received intervention.

TREATMENT FAILURE OF ACUTE COCCIDIOIDAL PNEUMONIA DUE TO PHARMACOKINETIC INTERACTION BETWEEN ITRACONAZOLE AND PHENYTOIN: A CASE REPORT

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INTRODUCTION

Coccidioidal pneumonia is part of the diverse forms of clinical presentation of the infection caused by *Coccidioides* spp. which range from asymptomatic to severe, this determined mostly by host immunity. Diagnosis is made by radiological findings, serology and microscopic observation of spherules in pulmonary secretions, though mycelial forms also have been reported. Itraconazole is the first option to treat pulmonary coccidioidomycosis. In this report, pharmacological treatment underwent a major fault that resulted in relapse and worsening of pulmonary symptoms of coccidioidal pneumonia due to pharmacokinetic interaction between itraconazole and phenytoin.

CASE REPORT

A 72-year-old housewife living in Mexico City, with a history of Type 2 DM, systemic arterial hypertension and recurrent seizures presented on December 2017 with cough, dyspnea, adynamia, diaphoresis and night fever. Radiological findings included a 16 mm cavity at the right, upper lobe. Direct exam of bronchalveolar lavage was negative for fungal structures, but culture resulted positive for *Coccidioides* spp. Itraconazole was initiated with an oral dose of 200mg/12h for 6 months. She was discharged and given phenytoin, metformin, amlodipine and rapid-acting insulin to treat comorbidities. On December 2018 she returned with similar symptoms, adding active hemoptysis and malaise. Chest X-ray showed paracardiac heterogeneous radiopacity in the right upper lobe, with an apparent occupied cavity. A strain of *Klebsiella* spp. was isolated from BAL culture. Thus, acute pneumonia was diagnosed and amoxiciline/clavulanate was initiated, without improvement, presenting hypoxemic status. In direct examination of sputum, abundant spherules were observed as well as thick-walled, septate hyphae. Culture isolates were confirmed as *Coccidioides* spp. by PCR. Phenytoin was discontinued as considering the drug interaction with itraconazole the cause of relapse and worsening of the infection.

DISCUSION

A clear worsening of the symptoms was observed despite being given the correct treatment according to therapeutic guides. This was caused by the intricate pharmacokinetic interaction between itraconazole and phenytoin, that results in the area under the concentration-time curve of itraconazole decreasing in more than 90% when administered with phenytoin (Cuttle *et al.,* 2000). Moreover, the finding of mycelial forms coincides with what was previously described by Muñoz *et al.,* (2008).

CAVITARY COCCIDIOIDOMYCOSIS AT CHEST CT: THE IMPACT OF TRIAZOLE THERAPY

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Introduction: Pulmonary cavities are seen in approximately 11-13% of patients with coccidioidomycosis. In the era of triazole antifungals, we hypothesized that coccidioidal cavities would close more quickly in patients treated with antifungals than those who did not receive such treatment.

Methods: We conducted a retrospective review of patients with cavitary coccidioidomycosis. The radiology information system was searched for chest CT reports containing the words “cavity” OR “cavitary” AND “cocci” or “coccidioidomycosis” between 1/1/2004 – 12/31/2014. We included patients diagnosed with proven, probable or possible coccidioidomycosis. We excluded patients with concurrent lung cancer or lung metastasis within 2 years of coccidioidomycosis diagnosis or patients infected with organisms that also cause or complicate lung cavities or those whose records or images were unavailable for review.

Results: The initial search identified 776 eligible patients, of whom 346 (44.6%) met criteria for cavitary pulmonary coccidioidomycosis. The median age was 58 years, and 183/346 (52.9%) were male and 286/346 (82.6%) were Caucasian. 88/346 (25.4%) had diabetes mellitus and 91/346 (26.3%) were immunocompromised. 258/346 (74.6%) were symptomatic, and cough, present in 170/258 (65.9%), was the primary symptom. Cavity closure occurred in 210/346 (60%), of which 134/210 (63.8%) received antifungal therapy without surgery whereas 34/210 (16.2%) of cavities closed in the absence of antifungal treatment. 45/346 (13%) patients underwent cavity resection and a subsequent cavity recurred in 6/45 (13.3%) of these patients. Median time to cavity closure for both the treated and untreated groups was 1.6 years (Ranges were 0.5 - 177 and 2 -129, respectively). Among the patients with symptomatic cavities, the median duration to cavity closure with antifungal therapy was 1.5 years, compared with 1.9 years in untreated patients. Patients with diabetes were less likely to experience cavity closure than non-diabetics [44/88 (50%) versus 166/258 (64%), p=0.02). Among symptomatic patients without diabetes or immunosuppression, the median time to cavity closure was 1.5 years if treated versus 1.9 years in the untreated group, p=0.01.

Conclusion: Compared with observation alone, administration of triazole antifungals was associated with reduced cavity closure times for symptomatic non-diabetic patients, but this effect was not observed in immunosuppressed or diabetic patients.

AN EXAMINATION OF CHRONIC PULMONARY COCCIDIOIDOMYCOSIS IN THE PRE-ANTIFUNGAL ERA

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INTRODUCTION There have been multiple studies to characterize pulmonary coccidioidomycosis (CM), yet these are often limited by small samples. The historical VA-Armed forces CM patient group provides a unique cohort of patients not treated with conventional antifungals to better characterize and describe chronic pulmonary CM with an emphasis on chronic nodules and cavities.

METHODS We conducted a retrospective study of 374 VA-Armed forces non-disseminated CM patients diagnosed between 1955-1958 and followed to 1966. Patients were included if they had a pulmonary nodule or a pulmonary cavity secondary to CM. Data was compiled to determine basic demographic information, complement fixation serology, and details regarding the nodules and cavities including number and size amongst others.

RESULTS The studied population had a median age of 34 with 97% men and 84% white. Eighty percent had no underlying pulmonary disease and concurrent tuberculosis was the most common comorbid pulmonary condition (11%). For patients who predominantly had cavities, the median complement fixation (CF) serology was 1:2 (interquartile range (IQR) negative-1:8). For patients who predominantly had nodules, the median CF serology was negative (IQR negative-1:2). The median number of pulmonary nodules was 1 with a median size of 1-1.9 cm. Sixty-nine percent of the nodules had a sharp, well defined border, while 10% had a calcified border. Eighty-six percent of the cavities were considered chronic. The median number of cavities was 1 with a median size of 3-3.9 cm. Only 45% of the cavity walls were thin, while 31% were thick and 19% were variable in size. Twenty-six percent of the cavities developed during acute infection with 46% developing without a prior history of primary infection. Twenty-nine percent of the cavities were stable in size, while 20% increased in size, 5% disappeared, 4% ruptured, and 2% decreased in size.

CONCLUSION This study helps further characterize chronic pulmonary nodules and cavities caused by CM. To our knowledge, this is the largest study of the natural history of chronic CM pulmonary cavities and nodules providing valuable descriptive features.

CASE PRESENTATIONS

A DEVASTATING CASE OF DISSEMINATED COCCIDIOIDOMYCOSIS IN A PREVIOUSLY UNDIAGNOSED AIDS PATIENT

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INTRODUCTION: Disseminated coccidioidomycosis (cocci) is a condition that most commonly presents in immunocompromised patients. While it is a severe infection, adequate and early treatment can have a fair prognosis in the absence of other comorbidities or if comorbidities are treated early. We are presenting the management of a patient with disseminated cocci complicated by hepatic and kidney failure secondary to advanced previously undiagnosed AIDS.

MATERIALS AND METHODS: Case report

RESULTS: A 47-year-old Hispanic male with a history of pulmonary cocci presented to our ED with two weeks of progressive shortness of breath. Review of records indicated that patient was diagnosed with pulmonary cocci two years prior, but was never tested for HIV. He was started on fluconazole, but his condition worsened one year later. He was then diagnosed with Tuberculosis in Mexico but after 5 days of treatement presented to our facility with worsening of productive cough, vomiting 10 times per night, and a 45-pound weight loss. He was found to be septic with multiorgan failure. Labs revealed WBC of 23.3, neutrophil count of 22.1 with 26% band, BUN of 92, creatinine of 6.47, total bilirubin 5.2, and INR 4.67. Viral hepatitis panel was negative. HIV viral load was over 600,000 copies/ml with absolute CD4 cells <20. Cocci complement fixation titer was 1:256. Imaging showed bilateral diffuse miliary pulmonary infiltrations. Empirical antibiotics, antituberculosis medication, liposomal amphotericin B, prednisone, and hemodialysis were initiated. Blood and Bronchoalveolar lavage grew coccidioidomycosis immitis. TB was ruled out and medication was adjusted accordingly. Patient was intubated due to hypoxia. Initiation of HIV treatment was a challenge due to his ChildPugh Score of 11, Class C, and HIV-associated nephropathy. Lamivudine, enfuvirtide, zidovudine, and etravirine were started. Patient continued to deteriorate and passed away in comfort care on hospital day 16.

CONCLUSION: In cases of combined liver and kidney failure the management of either coccidioidomycosis or HIV is perplexing. In the case of coinfection, this complexity becomes a real ordeal. Early diagnosis and suppression of HIV could prevent organ failure as a limiting factor for selection of appropriate treatment for other conditions.

FIRST REPORTED CASE OF OSTEOPOIKILOSIS MIMICKING DISSEMINATED OSSEOUS COCCIDIOIDOMYCOSIS

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INTRODUCTION: The clinical manifestation of coccidioidomycosis (cocci) infection ranges from asymptomatic disease to severe dissemination forms such as to bones. Diabetes a known risk factor in severity and dissemination. In the presence of coexistence of other osseous conditions, the diagnosis of dissemination becomes a difficult task. Here we are presenting a case of a severe form of pulmonary coccidioidomycosis co-infected with Methicillin-Resistant Staphylococcus Aurous (MRSA) with cavitation in the presence of underlying uncontrolled diabetes and congenital osteopoikilosis mimicking osseous dissemination.

MATERIALS AND METHODS: Case report

RESULTS: 40-year-old Hispanic woman with poorly controlled diabetes, previous history of MRSA bacteremia and amphetamine abuse presented to our facility with significant weight loss and glucose of 835 mg/dL. Imaging showed bilateral diffuse alveolar and nodular densities with a large cavitary lesion in the lingula. Serology confirmed the diagnosis of cocci with complement fixation (CF) of 1:4. Her sputum and bronchoscopy samples grew MRSA and Coccidioides immitis simultaneously. Blood cultures remained sterile. She was placed on liposomal amphotericin B and Linezolid. Her chest CT also showed diffuse medullary sclerotic lesions in the sternum, and bilateral clavicles and humerus bones. She had a high protein albumin gap above six gm/dl suspecting gammopathy. The bone survey showed similar findings in bilateral acetabulum, ischium, femurs, and tibias without lytic lesions and sparing spine. Technetium 99m bone scan also did not show any increased in uptake. She was diagnosed with osteopoikilosis. The patient continued to improve and was discharged home to complete 4 weeks of linezolid and will be continued on liposomal amphotericin B infusion. Her titers increased to 1:16 despite clinical improvement suggesting immune reconstitution syndrome.

CONCLUSION: Osseous dissemination of coccidioidomycosis should be suspected in the right clinical setting. However, the coexistence of other bone involvement such as hereditary disease, prior fractures, and metastasis makes the proper diagnosis difficult. A combination of different complementary imaging modalities should be used, and biopsies will remain the last resort.

A FATAL CASE OF COCCIDIOIDES MENINGOENCEPHALITIS WITH ISOLATED VENTRICULAR HYDROCEPHALUS AND INTERVENTRICULAR HEMORRHAGE

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INTRODUCTION: Disseminated coccidioidomycosis (cocci) to the central nervous system is amongst the most severe and devastating forms of this infection. Here we are presenting a patient with coccidioidomycosis meningoencephalitis with interventricular hemorrhage leading to ventricular hydrocephalus with over 30 foci of microinfarcts secondary to vasculitis due to basilar meningitis.

MATERIALS AND METHODS: Case report

RESULTS: A 42-year-old Hispanic man with a history of alcoholism and pulmonary cocci presented to our facility after he was found to be unresponsive by his roommate. On arrival, he was obtunded, nonverbal, moved extremities and opened eyes only to painful stimuli. His liver tests were consistent with alcoholic hepatitis. CT brain was negative. Lumbar puncture revealed opening pressure of 640, WBC of 670 (53% neutrophils, 17% lymphocytes), RBC 900, glucose of 12, and protein of 2700. Empirical antibiotics, fluconazole, and dexamethasone were started. CXR showed 15 mm left upper lobe nodule. He was intubated due to respiratory failure. Repeat CT brain showed new onset left ventricular hemorrhage and bilateral ventricular hydrocephalus. Cocci serology showed serum complement fixation (CF) of 1:64 and CSF CF of 1:32. Liposomal amphotericin B and voriconazole were started. MRI brain confirmed the presence of blood in both ventricles, aqueduct of Sylvius, and the fourth ventricle suggesting a clot within the foramen of Monro as the etiology behind acute bilateral ventricular hydrocephalus. MRI revealed over 30 diffuse non-enhancing microinfarcts and diffuse and basilar leptomeningeal enhancements. Ommaya reservoir was suggested to start intrathecal amphotericin but deemed to be too risky. Subsequently, patient's reflexes became diminished and absent on hospital day 10. His level of care was changed to comfort care, and he passed away of hospital day 12.

CONCLUSION: Hydrocephalus and vasculitic infarcts are commonly seen in disseminated central nervous system coccidioidomycosis. To the best of our knowledge, hemorrhagic ventriculitis with acute isolated bilateral ventricular hydrocephalus is rarely seen. Early diagnosis and treatment are crucial to prevent morbidity and mortality associated with this form of infection.

CROUP CAN BE “COCCI”, TOO: A CASE OF A 9-MONTH-OLD BOY WITH SUBGLOTTIC COCCIDIOIDOMYCOSIS MASS PRESENTING AS PERSISTENT CROUP

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INTRODUCTION: Laryngeal coccidioidomycosis is rare and typically presents with upper airway symptoms. Predominant reported cases are seen in adults. Here we present a nine-month-old infant with persistent croup symptoms secondary to laryngeal coccidioidomycosis.

CASE REPORT: Patient is a nine-month-old Hispanic boy from Bakersfield CA, presented with a two month history of recurrent laryngotracheobronchitis (croup). The respiratory symptoms started with persistent nonproductive barky cough, inspiratory stridor, hoarseness and a low-grade fever. Initial diagnosis was croup but further workup showed right lower lobe and right middle lobe pneumonia. Patient received two courses of antibiotics, several doses of racemic epinephrine, inhaled and oral steroids over a four months’ time with only few days of remission per treatment course. Radiographic imaging showed subsequent subglottic narrowing and retropharyngeal widening. Patient was transferred for higher level of care where he underwent direct laryngoscopy and bronchoscopy. Laryngoscopy showed an extrapulmonary laryngeal mass encompassing majority of the true vocal cords (TVC) while obstructing the airway and the mobility of the surrounding structures. Biopsies of the laryngeal mass revealed Coccidiodes spherules with endosporulation. Bronchoscopy was essentially negative. Initial serology was negative but repeat serum complement fixation titer (CF) came back as 1:32 with a serum Immunodiffusion positive for IgG. Patient underwent tracheostomy and started on Amphotericin B. One month later, repeat laryngoscopy showed good TVC movement with no evidence of laryngeal mass; and treatment was switched to fluconazole 120 mg daily. Decannulation of tracheostomy was performed two months after placement. The patient recovered well without swallowing difficulties, speech impairment, hoarseness, stridor or respiratory distress. His most recent serum coccidioidomycosis CF improved to 1:8. He continues to take daily fluconazole 120mg.

Conclusion: Clinicians should be aware of laryngeal coccidioidomycosis in endemic region as one of the differential diagnosis of croup.

A RARE CASE OF DISSEMINATED COCCIDIOIDOMYCOSIS OF THE GALLBLADDER

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INTRODUCTION: Disseminated Coccidioidomycosis (cocci) of the gallbladder is an extremely rare entity, with only one other case reported in the literature.

MATERIAL AND METHODS: A retrospective case report

RESULTS: A 60-year-old Hispanic male with Diabetes mellitus type 2 and previous right wrist disseminated osseous cocci from past presented with acute onset dyspnea, right upper quadrant (RUQ) pain, and progressively worsening fatigue in the last two weeks. Laboratory studies revealed diabetic ketoacidosis. Thereafter, the patient began to develop fevers, hiccups, non-productive cough, and worsening RUQ pain, not responding to empiric broad-spectrum antibiotics. Chest x-ray showed a lingular patchy alveolar density and a 7 mm left mid-lung pulmonary nodule. Computed Tomography revealed numerous cavitary pulmonary nodules in the chest, in addition to a mildly distended gallbladder containing stones, and minimal wall thickening. Gallbladder sonogram demonstrated sludge, calcified stones in the gallbladder, and a 5.6 x 3.5 cm multiloculated pericholecystic fluid collection. Transcutaneous drainage of the pericholecystic fluid collection was performed. Due to discordance between the volume of fluid and the size of the pericholecystic fluid collection seen on imaging, a fistulogram was performed. Fistulogram demonstrated a contained pericholecystic abscess with a sinus tract to the gallbladder, suggesting that a sinus tract had been formed secondary to a chronic underlying manifestation. Subsequently, a cholecystostomy drain was placed into the gallbladder and 10 cc of turbid bilious fluid was evacuated; fungal culture grew Coccidioidomycosis immitis. Cocci serology showed a complement fixation of 1:16. Whole body bone scan showed increased uptake at the right wrist. He was started on liposomal Amphoteric B and continued at the infusion center for 12-week duration. He continues to have a cholecystostomy tube until delayed cholecystectomy is performed.

CONCLUSION: Dissemination of coccidioidomycosis to the gallbladder is very rare. Despite medical therapy, there is a lack of evidence for the best timing for cholecystectomy.

COCCIDIOMYCOSIS MENINGITIS CAUSING SYRINGOMYELIA DUE TO TYPE I CHIARI MALFORMATION: TREATMENT OUTCOME OF A CASE WITH 14 YEAR FOLLOW-UP

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Infectious meningitis is a common cause of hydrocephalus that may require ventriculo-peritoneal shunting. However, meningitis causing symptomatic syringomyelia from associated arachnoiditis is rare. This report describes 14 year follow-up of a patient with coccidiomycosis meningitis where surgical treatment of an unrecognized underlying Chiari I malformation resulted in symptomatic and radiographic resolution of the syringomyelia. Less invasive treatment for delayed hydrocephalus occurring years later resulted in sustained symptomatic and radiographic resolution. A pictorial essay and neurosurgical rationale for treatment will be presented.

Case Summary:

A 32 year-old Filipino female was diagnosed with coccidiomycosis meningitis in 2004. Fluconazole 400 mg/day relieved symptoms of headaches and nausea. 2 years later she developed recurrent headaches, nausea and vomiting. Contrasted T1 MRI imaging of the entire neural axis showed marked, diffuse enhancement of the subarachnoid space simulating T2 weighted CSF hyperintensity. Symptomatic support and increasing fluconazole to 400 mg bid improved symptoms. 6 months later, she was re-admitted for acute worsening of headaches. Her antifungal treatment was changed to IV voriconazole 288 mg q 12' for 6 weeks followed by voriconazole 200 mg po bid.

1 year later, she developed left facial, neck and upper extremity sensory loss and paresis. MRI imaging revealed extensive cervical and thoracic cord edema, syringomyelia and diffuse arachnoiditis. Close inspection revealed a previously unrecognized Chiari I malformation. A suboccipital craniectomy, C1 laminectomy and duraplasty were performed to decompress the cranio-cervical junction. Her symptoms resolved with progressive resolution of syringomyelia and cord edema.

7 years later, she developed acute hydrocephalus. Serial lumbar punctures and increasing voriconazole to 400 mg po bid was performed in anticipation of shunt surgery. Fortuitously, prompt resolution of symptoms and ventriculomegaly occurred 2 weeks later.

The patient remains asymptomatic at 14 years follow-up with continued resolution of syringomyelia and hydrocephalus.

Conclusions:

1) Coccidiomycosis meningitis patients with cord edema, and/or syringomyelia, should be evaluated for Chiari malformation, or obstruction of the cranio-cervical junction from arachnoiditis.

2) Clinical and radiographic resolution can occur after standard Chiari decompression surgery.

3) Symptomatic mild-moderate hydrocephalus can be reversed with serial high volume lumbar punctures with concurrent medical management.

ISAVUCONAZOLE AS SALVAGE THERAPY IN PEDIATRIC REFRACTORY COCCIDIOIDAL MENINGITIS CASE

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Background:

Coccidioidal meningitis remains difficult to treat. The newer triazole, isavuconazole has demonstrated good efficacy in invasive fungal disease with less side effects than other azoles. We describe a case of refractory pediatric coccidioidal meningitis with disease stability on isavuconazole after failing otherantifungals.

Case Description:

An 11 year old previously healthy female developed coccidioidal meningitis at age 6. She did well for one year on fluconazole, and then developed back pain and headaches. MRI showed new cerebral and lumbosacral spinal lesions without vertebral disease. CSF had pleocytosis, low glucose and coccidioidal complement fixation (CF) titer of 1:2. She was started on oral voriconazole and intrathecal (IT) amphotericin. IT amphotericin was discontinued after six months due to side effects. Symptoms recurred within two months with new cerebral lesions on MRI. Treatment was changed to 3 times/week IV liposomal amphotericin and oral posaconazole. After 9 months, CSF studies were stable with negative coccidioidal immunodiffusion (ID) and CF titers. Liposomal amphotericin B was held due to renal insufficiency while posaconazole continued. Ten weeks later she presented with worsening headaches and vomiting. An MRI revealed a subarachnoid bleed secondary to progressive disease in the cisterns in the posterior fossa with stable cerebral and spinal lesions. Serum CF titer was negative but CSF ID was positive for IgG with negative CF titers. CSF coccidioidal antigen was 3.69, suggestive of disease relapse. MRA and MRV showed no evidence of aneurysm or vasculitis. Liposomal amphotericin was restarted with the continued posaconazole for an additional 15 months. Because of renal insufficiency she was changed to isavuconazole monotherapy, 200 mg/day initially, later changed to 100 mg/day due to severe nausea and headaches. She has been stable on this regimen for 10 weeks without symptoms with stable MRI.

Conclusions:

Isavuconazole has been approved for use in invasive aspergillosis and mucormycosis in adults. However, current knowledge is limited about its use in children. This is the first reported pediatric case of refractory coccidioidal meningitis treated with isavuconazole. Prospective clinical trials are needed in order to evaluate the pharmacokinetics and safety of isavuconazole in children.

Extrapulmonary coccidioidomycosis presenting as peritonitis

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Purpose of study:

While coccidioidomycosis most commonly presents as a pulmonary infection, dissemination can occur in rare number of cases. Intraabdominal dissemination have been reported but very few cases had peritoneal involvement. This is a case of disseminated coccidioidomycosis presenting as peritonitis.

Methods used:

Retrospective case report

Case Description:

23 year old Hispanic male with history of inguinal hernia repair presented to an outside hospital with one month history of fever, weight loss, blood in stool, abdominal pain and distension. He was discharged after paracentesis without any further treatment. He presented to another hospital with more severe abdominal pain and distension. Imaging found recurrent abdominal ascites with omental caking, a loculated left sided pleural effusion with volume loss, diffuse mediastinal lymphadenopathy, and splenomegaly. Out of concern for lymphoma, a cervical lymph node biopsy was performed, which instead showed spherules with endosporulation consistent with coccidioidomycosis. Intravenous liposomal amphotericin B was started three times a week. After three weeks, he developed worsening abdominal symptoms and was transferred to our institution for higher level of care. Upon arrival his coccidioidal complement fixation (CF) titers were greater than 1:512. He developed small bowel obstruction with a large pelvic abscess and progression of ascites. Catheters placed into pelvic abscess drained purulent fluid that grew *C. immitis*, *Escherichia coli*, and *Bacteroides ovatus*. Small bowel obstruction improved with abscess drainage and antibiotic therapy. After seven hospital days he was discharged with daily outpatient treatment at our infusion center, ambulating and tolerating a regular diet. His amphotericin treatment was increased to daily infusions for 14 days, then tapered to three times a week for 12 weeks, and then transitioned to isavuconazole. His most recent CF titers improved to 1:256.

Conclusion:

Physicians in areas endemic to coccidioidomycosis should be aware of the possibility of abdominal and peritoneal dissemination as the presenting symptom of disseminated coccidioidomycosis. Surgical intervention should be avoided by all means.

Multifocal osseous coccidioidomycosis masquerading as multiple myeloma

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Purpose of study

Coccidioidomycosis commonly manifests in the lung but can disseminate to bone and other tissues. Multiple myeloma is a plasma cell cancer that presents as lytic bone lesions in the spine and skull. We present a case of osseous coccidioidomycosis that initially presented with lytic bone lesions.

Methods of study:

Retrospective case report

Summary of results

35-year-old homeless, cachectic male with a polysubstance abuse presented after an assault to the head and neck. Initial CT neuroimaging incidentally revealed multiple destructive lytic lesions. Follow up T1 weighted MR neuroimaging demonstrated multiple gadolinium enhancing destructive calvarial, cervical, thoracic, and lumbar spine lesions. Initial chest x-ray was benign except for a distal clavicular lesion. CT imaging found a thin walled cavitary lesion in the right upper lobe. At this point, lytic bone lesions, mild microcystic anemia and cachexia raised concern for plasma cell dyscrasia such as multiple myeloma in addition to coccidioidomycosis. However, urine and serum sent for protein electrophoresis and light chain analysis were consistent with chronic inflammation. Instead, coccidioidomycosis serum immunodiffusion were IgM and IgG reactive and immunofixation was reactive to 1:256 titration. Further history was obtained, revealing that one week prior, he was at another hospital where a bone biopsy found endosporulating spherules without evidence of malignancy. Patient was initially started on fluconazole 600mg PO BID and liposomal amphotericin B, but subsequently left AMA. Meanwhile, he was restarted on daily intravenous liposomal amphotericin B 5mg/kg for 18 days with plan for three infusions weekly for 12 weeks as an outpatient. Two days after discharge he represented with neck pain. CT and MRI neuroimaging found pathological fractures of C5 and bilateral perched facet of C5 to C6. He underwent C5 corpectomy and C4 to C6 spinal fusion where pathology redemonstrated endosporulating spherules. Postoperatively, patient left AMA again and has been lost to follow up ever since.

Conclusion

Axial lytic bone lesions with anemia and weight loss in the middle aged may initially suggest multiple myeloma. Physicians in areas endemic for coccidioidomycosis should be aware of atypical presentation of dissemination that may masquerade as other more commonly described diseases.

CONCOMITANT CENTRAL NERVOUS SYSTEM TOXOPLASMOSIS AND SERONEGATIVE DISSEMINATED COCCIDIOIDOMYCOSIS IN A NEWLY DIAGNOSED ACQUIRED IMMUNE DEFICIENCY SYNDROME PATIENT

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Introduction

Opportunistic infections are a major cause of morbidity and mortality in acquired immune deficiency syndrome (AIDS). We describe a fatal case of disseminated coccidioidomycosis (Cocci) and central nervous system (CNS) toxoplasmosis in a newly diagnosed AIDS patient.

Case Description

A 33 year-old Hispanic male with no medical history presented to an outside hospital with headaches and was diagnosed with a 2.7cm ring-enhancing intracranial lesion in the right temporal lobe. He was subsequently transferred to our facility for neurosurgical intervention. Post-operatively, he was febrile and transferred to the medicine team. He was screened and diagnosed with AIDS with CD4 count of <20cells/microL. Antiretroviral and CNS toxoplasmosis treatments were started. Comprehensive screening in AIDS host, including cocci serology, was negative except high IgG titers for toxoplasmosis. Histopathology of the brain lesion confirmed the diagnosis. Further investigation revealed that the patient was made aware of HIV diagnosis two years prior but remained in denial. He was discharged after fever resolved but was readmitted one week later with persistent fevers at which time he was found to have a new left upper lobe infiltration. Broad-spectrum antibiotics plus fluconazole were started and he was placed on air born precautions until tuberculosis could be ruled out. Cocci serology was again negative. His condition deteriorated with hypoxemia and development of diffuse miliary pattern revealed by CT of the chest. Bronchoscopy was arranged but hypoxemia worsened and prompted intubation. Bronchoalveolar lavage after intubation showed spherules and blood culture grew fungus resembling *Coccidioides immitis*. Antifungal treatment was changed to liposomal amphotericin B but the patient developed severe acute respiratory distress syndrome (ARDS), went into cardiac arrest, and passed away.

Conclusion

Impaired immune function, such as defects in the IL-12/IFN-γ pathway and T-helper 17-mediated response, is associated with increased severity of coccidioidomycosis. In HIV hosts, negative serology can be seen in up to 25% of cases. Therefore, other diagnostic modalities should be initiated promptly and simultaneously. Fungemia and ARDS are both associated with very high mortality in coccidioidomycosis.