PROCEEDINGS OF THE COCCIDIOIDOMYCOSIS STUDY GROUP
61st ANNUAL MEETING
in collaboration with the
7th INTERNATIONAL
COCCIDIOIDOMYCOSIS SYMPOSIUM

August 10-13, 2017

Stanford, CA

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Stanford University School of Medicine

Li Ka Shing Center

Stanford, California

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POSTER ABSTRACT PRESENTATION AGENDA
HOSTED AT LI KA SHING AUDITORIUM INDOOR VENUE

August 11 and 12, 2017

Moderators: CSG Program Committee

August 11, 2017
7:00-8:00 A.M. Breakfast, Registration, Poster Set-up

10:00-10:30 A.M.
12:30-1:30 P.M.
3:30-4:00 P.M.
Poster Visitation Times - designated times will be attended by abstract presenters. Posters may be viewed all day.

August 12, 2017
7:00-8:00 A.M. Breakfast, Registration, Poster Set-up

10:00-10:30 A.M.
12:30-1:00 P.M.
2:30-3:00 P.M.
Poster Visitation Times - designated times will be attended by abstract presenters. Posters may be viewed all day.

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ENHANCED SURVEILLANCE FOR COCCIDIOIDOMYCOSIS IN STATES WHERE IT IS NOT HIGHLY ENDEMIC, 2016

Benedict K[1], Weinberg MP[2], Ireland M[3], Peck SJ[4], Gruninger RJ[5], Chen, L[6], Perez-Lockett K[7], Denny L[8], Gibbons-Burgener S[9], DeBess E[10], Warren K[11], Serrano JA[12], Turabelidze G[13], Lepp A[14], McCotter O[1], Jackson BR[1]

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INTRODUCTION: Effects of coccidioidomycosis on patients in Arizona and California have been relatively well-characterized. However, features of coccidioidomycosis in residents of non-highly-endemic states have not been described in detail. Coccidioidomycosis is nationally notifiable, but the National Notifiable Diseases Surveillance System only captures basic coccidioidomycosis patient demographic information. We conducted enhanced surveillance in states where coccidioidomycosis is reportable to better describe the epidemiology, diagnosis, and outcomes of these patients to help inform surveillance and guide awareness and educational efforts.
METHODS: In 14 states (Louisiana, Michigan, Minnesota, Missouri, Montana, Nevada, New Mexico, North Dakota, Ohio, Oregon, Pennsylvania, Utah, Wisconsin, and Wyoming), state and local health department personnel identified cases with the Council of State and Territorial Epidemiologists case definition through routine surveillance during 2016 and interviewed consenting patients using a standardized questionnaire. Coccidioidomycosis diagnostic test information was extracted from health departments' surveillance databases. Data were compiled at CDC.
RESULTS: Total, 186 coccidioidomycosis patients were interviewed. Most (59%) were male, 151 (89%) were white, and the median age was 65 years (range, 7–91). Cough (n=121, 65%), fatigue (n=116, 62%), and fever (n=85, 46%) were commonly reported symptoms. Median time from symptom onset to seeking healthcare was 5.5 days (range, 0–488), and median time from seeking healthcare to diagnosis was 38 days (range, 0–1,654). One-hundred and fifteen patients (70%) reported having been diagnosed with another condition before being tested for coccidioidomycosis; of those, 99 (83%) were prescribed antibiotics. Seventy-seven (43%) were hospitalized, 115 (68%) were treated with antifungal medications, and 117 (71%) said that their illness interfered with daily activities (for a median of 40 days [range 2–1,080]). In the 4 months before symptom onset, 97 (52%) traveled to Arizona and 21 (11%) traveled to California. Eighty-seven (51%) patients knew about coccidioidomycosis before being diagnosed with it. Fifty-three patients (29%) had culture-positive coccidioidomycosis.
CONCLUSIONS: Coccidioidomycosis causes substantial morbidity in residents of non-highly-endemic states, similar to previous studies of Arizona residents. The high proportion of patients diagnosed by culture (compared with <10% in Arizona) suggest that less severe cases likely go undiagnosed or unreported. Even among recognized cases, delays in diagnosis and unnecessary antibiotic use were common. Improved healthcare provider and public awareness of coccidioidomycosis outside highly-endemic areas is needed.

PROTEOGENOMIC RE-ANNOTATION OF *COCCIDIOIDES POSADASII* STRAIN SILVEIRA

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Introduction

Proteomic analyses using mass spectrometry are increasingly being used in the diagnosis of microbes, the identification of drug targets, and in understanding host-pathogen interactions. As protein databases are largely computationally derived from the genome, an accurate genome annotation is vital. Although *C. posadasii* strain Silveira is one of the most commonly used laboratory strains of *Coccidioides*, the current genome has been sequenced with less coverage and with higher gap lengths than less commonly used strains. Thus, the aims of this study were to provide protein-based evidence upon which to re-annotate of the genome of *C. posadasii* strain Silveira.

Methods

Proteins present in lysates and filtrates of *in vitro* grown mycelia (coccidioidin) and parasitic phase spherules (spherulin) from *C. posadasii* strain Silveira were analyzed using a GeLC-MS/MS method. Acquired spectra were processed with a proteogenomics workflow comprising the Broad Institute proteome database (http://broadinstitute.org), a 6-frame translation of the Silveira genome (created using EMBOSS: sixpack) and an *ab initio* gene prediction tool named AUGUSTUS (http://augustus.gobics.de) prior to validation against published ESTs.

Results

This study provides evidence for 837 genes expressed at the protein level, of which 169 proteins (20.2%) were putative proteins and 103 (12.3%) were not annotated in the Silveira genome. Additionally, 275 novel peptides were derived from intragenic regions of the genome and 13 from intergenic regions, resulting in 172 gene refinements. Furthermore, we are the first group to report a translationally active retrotransposon in a *Coccidioides spp*.

Conclusions

Our study reveals that the currently annotated genome of *C. posadasii* strain Silveira needs refinement, which is likely to be the case for a number of the other *Coccidioides spp.* strains. These refinements to the Silveira genome are important for researchers pursuing diagnostic markers or protein expression to drugs, as without such reannotation of the Silveira genome, researchers could be blind to observing certain proteins in a sample, purely because the proteins are not available in the given databases.

IDENTIFICATION OF VALLEY FEVER BIOMARKERS USING LASER CAPTURE AND LC-MS/MS OF HUMAN LUNG TISSUES

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Introduction

The current mainstay diagnostic methods for Valley Fever (VF) involve antibody measurement. However, ~20% of patients do not produce detectible antibody responses to VF infections and many infected individuals have delayed responses. Alternative approaches for diagnosis of this fungal infection are thus needed. One such potential method is to measure antigen leaked from infected tissues (usually lungs) into other body fluids during infection. Herein we describe a label-free tissue proteomics pipeline for the identification of potential VF biomarkers from patient lung tissues and compare the proteins expressed *in vivo* with *in vitro*-grown mycelia and spherules.

Methods

Laser capture microdissection (LCM) was performed on *Coccidioides sp.* spherules extracted from paraffinized formalin fixed (PFFE) lung tissues from a patient with VF, followed by a modified filter-aided sample preparation prior to nanoscale liquid chromatography and high resolution mass spectrometry on a Thermo QExactive. *In vitro*-grown lysates of both the mycelial and parasitic phases of *Coccidioides posadasii* strain Silveira were used as comparative controls, using a GeLC-MS/MS method.

Results

This pipeline identified on average 2,085 peptides corresponding to 484 proteins from sub-microgram amounts of protein extracted from the patient lung tissues. Additionally, 475 proteins were found in the *in vitro*-grown mycelia and 685 proteins in the *in vitro*-grown spherules. A number of significantly differentially expressed proteins were identified in each sample group, elucidating differences in biological processes and molecular function gene ontologies.

Conclusion

In vitro and *in vivo* grown spherules in human lung tissue show significant gene expression differences at the protein level. LCM of PFFE lung tissues from infected patients can help elucidate the highly abundant proteins expressed *in vivo*, which have the potential to be used to identify biomarkers of infection.

EPIDEMIOLOGY OF COCCIDIOIDOMYCOSIS OUTBREAKS REPORTED WORLDWIDE, 1940-2015

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INTRODUCTION

Although most coccidioidomycosis cases are sporadic, outbreaks provide insight into its clinical and environmental features, high-risk activities, and the geographic range of *Coccidioides*. We reviewed documented coccidioidomycosis outbreaks to identify common features.

METHODS

We searched published English-language literature using combinations of the terms "coccidioides" or "coccidioidomycosis" and "epidemic," "outbreak," or "cluster." An outbreak was defined as ≥2 coccidioidomycosis cases linked to a common source in space and time, and an outbreak required ≥1 case of coccidioidomycosis.

RESULTS

We identified reports of 48 coccidioidomycosis outbreaks that resulted in 1,467 cases during 1940–2016. Outbreak size ranged from 2–379 cases (mean 30, median 10). The two largest outbreaks, comprising 582 (40%) cases, resulted from an earthquake and a dust storm. Forty-one (85%) outbreaks were associated with environmental exposures, four were related to laboratory exposures, two involved transmission through organ transplantation, and one was a nosocomial outbreak. Thirty-one (65%) outbreaks reported total numbers of people possibly exposed, ranging from 2–676,667 (median 27), resulting in clinical attack rates ranging from 0.03–100% (mean 44%, median 43%). Twenty-one (44%) outbreaks comprising 566 (39%) cases were travel-associated. Twenty-five (52%) outbreaks were associated with occupational exposures, 11 (23%) outbreaks were associated with the military, and five (10%) outbreaks were among incarcerated populations. Of 35 (73%) outbreaks with hospitalization data, 543 (43%) patients were hospitalized. Eighteen (2%) patients in 28 (58%) outbreaks died. Among 38 (79%) outbreaks that reported whether the outbreak revealed previously unknown information about endemicity, 12 (32%) revealed a new endemic area.

CONCLUSION

Coccidioidomycosis outbreaks are a key data source regarding modes and locations of exposure. Outbreaks have revealed new information about the geographic range of *Coccidioides* and highlight risks for travelers, outdoor workers, military personnel, and incarcerated people. Many more outbreaks are likely not recognized, not reported to public health, not investigated, or not published. Coccidioidomycosis outbreaks can be difficult to detect and challenging to prevent given the unknown effectiveness of environmental control methods and personal protective equipment. Therefore, increased awareness of coccidioidomycosis outbreaks among public health professionals, healthcare providers, and the public is needed.

THE ROLE OF EXTRACORPOREAL MEMBRANE OXYGENATION IN SEVERE PULMONARY COCCIDIOIDOMYCOSIS

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Introduction

Diffuse pulmonary coccidioidomycosis may lead to rapid deterioration and death. Extracorporeal membrane oxygenation (ECMO) has been successful in other endemic mycoses, including histoplasmosis and blastomycosis. We review our experience with severe pulmonary coccidioidomycosis managed with ECMO.

Methods

A review of three cases of severe pulmonary coccidioidomycosis managed with ECMO at Regional Medical Center of San Jose (RMCSJ), a tertiary care referral center located in San Jose, California, was conducted. Patient characteristics, clinical course, medical management, complications and outcome were reviewed in detail.

Results

Between January, 2015 and May, 2017, twenty seven patients were treated with ECMO in RMCSJ for a variety of conditions, including respiratory infections in eleven cases (41%), three of whom had severe pulmonary coccidioidomycosis. Our cases were males, aged 30-53 years, without immunosuppressive condition or therapy, referred from endemic areas with culture-proven coccidioidomycosis. Two had diabetes mellitus, and all were obese. They developed rapidly progressive respiratory failure with bilateral lung infiltrates requiring mechanical ventilation including prone modality. ECMO was administered for refractory hypoxic respiratory failure from acute respiratory distress syndrome (ARDS) unresponsive to 2-5 days of antifungal therapy (fluconazole in 2, and fluconazole with amphotericin in the other). Pre-ECMO ventilator days ranged from 4-12; ECMO days 8-16, and post-ECMO ventilator days from 8-39. Complications included pneumonia, acute renal failure, transient encephalopathy with delirium, and critical illness myopathy. All received liposomal amphotericin while on ECMO and transitioned to fluconazole or itraconazole. Two required tracheostomy with transfer to a rehabilitation center. All required prolonged hospitalization (range 40-63 days), and survived.

Conclusion

ECMO was life-saving for severe pulmonary coccidioidal ARDS. Common complications in our patients treated with ECMO included pneumonia, transient encephalopathy and critical illness myopathy. They received liposomal amphotericin while on ECMO were transitioned to azole therapy. All required prolonged hospitalization with physical therapy, Further studies on the optimization of care of patients critically ill with pulmonary coccidioidal ARDS, and the pharmacokinetics of antifungal agents during ECMO, are required.

THE SPATIAL DISTRIBUTION OF REPORTED COCCIDIODOMYCOSIS IN THREE ARIZONA COUNTIES, 2013–2015

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Introduction

Two-thirds of all coccidioidomycosis cases reported nationally reside in Arizona. Relatively little is known about the spatial occurrence of coccidioidomycosis at scales smaller than the county level. Environmental sampling studies suggest that the distribution of *Coccidioides* spp. growth sites is non-uniform, and other states have identified point-source outbreaks. Identifying areas of increased incidence may provide greater insight into variation in risk of coccidioidomycosis and inform prevention strategies. We describe the spatial distribution of coccidioidomycosis cases residing in Maricopa, Pima, and Pinal counties between 2013 and 2015.

Methods

Addresses for laboratory-confirmed coccidioidomycosis cases reported to the Arizona Department of Health Services between 2013 and 2015 were geocoded and aggregated at the census tract level. Census tract population estimates were obtained from the American Community Survey 2011–2015 five-year estimates. Annual tract-level incidence rates were calculated using empirical Bayes methods to produce stable estimates. Clustering was assessed at the tract-level using global and local measures of spatial clustering (Moran's I, Local Indicators of Spatial Autocorrelation, Kulldorff's spatial and space-time scan statistics). Tract-level counts were averaged across years for the spatial scan statistic analysis. Descriptive mapping and statistical analysis were performed in GeoDa, SaTScan, Google Earth, and ArcMap.

Results

13,717 cases (76% of reported cases) were successfully geocoded. Census tract case counts ranged from zero to 25 with a median of three cases per tract. Incidence rates ranged from 16 to 795 cases per 100,000 person-years. Significant spatial autocorrelation was observed each year (Moran's I range: 0.20–0.26, p=0.001), suggesting that areas of high and low incidence cluster together. Age-adjusted spatial scan statistic analysis identified three clusters of higher than expected incidence (relative risk range: 1.22-1.65) and t wo clusters of lower than expected incidence (relative risk range: 0.68-0.73).

Conclusion

The distribution of reported coccidioidomycosis in these three countries is non-random, and census tract rates vary markedly within this highly endemic area. Spacial clustering persists after accounting for the age distribution of the population. Further analysis is required to identify factors associated with elevated census tract incidence rates.

PERITONEAL COCCIDIOIDOMYCOSIS: A TRIAD OF PERITONITIS, OMENTAL NODULES, AND EOSINOPHILIA

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Introduction

Less than 1% of coccidioidomycosis (CM) cases disseminate following an initial pulmonary infection. Systems most commonly affected include skin, bone, and meninges. Previous cases describing peritoneal involvement are rare, ranging from an asymptomatic inguinal mass to acute peritonitis. We report the first documented case of peripheral eosinophilia in a patient with peritonitis and omental nodularity due to disseminated peritoneal CM.

Case Presentation

A 50-year old Filipino man with poorly controlled type 2 diabetes mellitus presented with 4 days of fever, abdominal pain and abdominal distention. He endorsed unintentional weight loss of 30lbs over the last year as well as a chronic cough. The physical exam was notable for bibasilar lung crackles and abdominal distention with diffuse tenderness to palpation and rebound. Labs revealed a white blood cell count of 9.9K/μL with an absolute eosinophil count (AEC) of 1.7 K/μL (17.4%). A chest x-ray showed a left lower lobe lung consolidation. Abdominal CT demonstrated large ascites without cirrhosis and innumerable nodules studding the omentum. Ascitic fluid contained >6,000 leukocytes (53% neutrophils, 30% lymphocytes, 10% macrophages, 5% eosinophils). Fluid cytology was negative for malignancy. Peritoneal and sputum studies for tuberculosis returned negative. Serologies for Cryptococcus, Strongyloides, HIV and Hepatitis C were also negative. *Coccidioides* serologies returned positive for IgG and IgM antibodies with a complement fixation titer of 1:2. Ascitic fluid grew white mold identified as *Coccidioides immitis*. The patient was discharged on Fluconazole 400 mg PO daily for 12 months.

Conclusion

Our patient's initial presentation was highly concerning for malignancy. While intra-abdominal coccidioidomycosis (IAC) can mimic peritoneal carcinomatosis, to our knowledge, this is the first reported case of a patient with ascites and omental nodularity where peripheral eosinophilia provided an important diagnostic clue for the presence of disseminated *Coccidioides*. IAC is rare, even in endemic areas, and clinicians should be aware of this atypical presentation to avoid misdiagnosis.

COCCIDIOIDOMYCOSIS PRESENTING AS TEMPOROMANDIBULAR JOINT SEPTIC ARTHRITIS

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Introduction

Coccidioidomycosis is endemic primarily to the Southwest United States, as well as parts of Mexico and South America. Infection normally begins in the lungs after inhalation of arthroconidia characteristic to *Coccidioides immitis* (found in California) and *Coccidioides posadasii* (found in Arizona and elsewhere). Rarely, infection can progress to pneumonia, localized cavitary lesions and in even rarer instances to the meninges, bone and joints. Initial presentation as temporomandibular joint (TMJ) infection has rarely been described.

Case findings

A 43-years-old previously healthy African American inmate presented to a California prison's infirmary with left temporomandibular joint (TMJ) tenderness and swelling, progressing over 4 weeks. He also reported fever on and off, 30 lbs weight loss and back pain. He denied respiratory, GI, GU symptoms or headache. He received Augmentin without any improvement so he was transferred to an outside hospital.

Clinical course

A maxillofacial CT scan was performed and suggested septic arthritis and probable osteomyelitis of left TMJ, so patient was transferred to Banner-University Medical Center Phoenix. Past medical/surgical history as well family history were noncontributory. He denied smoking, alcohol, drug abuse or ever visiting Arizona. On admission, the physical exam was unremarkable except for mild swelling and tenderness at the left TMJ area. He was febrile (38.4^{o}C), with pertinent labs showing a WBC count of 13.4 k/mm^3 and normal differential, an ESR of 98 mm/hr and CRP of 161 mg/L. He was initially placed on vancomycin and piperacillin/tazobactam, but continued to have persistent fever and pain at the left TMJ area.
CT scan revealed multiple areas of erosive, lytic changes at the T7-12 vertebrae, the thoracic ribs, lumbar spine and pelvis (iliac bone), raising concern for metastatic cancer. CT scan of the chest showed miliary micronodules throughout both lungs.

Outcome

A biopsy of the iliac crest showed necrotizing granulomatous inflammation with abundant spherules. Culture from a TMJ aspirate grew *Coccidioides* species. Serologies for *Coccidioides* were positive by EIA and immunodiffusion; Complement fixation titer was >1:256. Patient was placed on fluconazole at 800mg/day and became afebrile with improvement of the left TMJ pain and swelling. He was transferred back to the prison infirmary and lost to follow-up.

Conclusion

Coccidioidomycosis of the mandibular bone/TMJ has rarely been reported. This case of disseminated coccidioidomycosis presenting initially as TMJ septic arthritis shows the great scope of clinical presentations and how one should always include coccidioidomycosis in the differential diagnosis in patients living in or having visited endemic areas.

DECTIN-1 AND DECTIN-2/CARD9 SIGNALING PATHWAY IS REQUIRED FOR VACCINE IMMUNITY OF A MULTIVALENT VACCINE AGAINST COCCIDIOIDES POSADASII INFECTION

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Introduction

Coccidioidomycosis is a formidable threat to 30 million residents in the Southwestern United States, leading to a high priority to develop a vaccine against this disease. Vaccine immunity against Coccidioides infection requires $CD4^+$ T helper (Th) lymphocytes, particularly Th17 cells. We have created a recombinant, chimeric polypeptide antigen (rCPA1) that is composed of 3 previously characterized vaccine antigens and 5 human T-cell epitopes. The multivalent rCPA1 was loaded into glucan-chitin particles (GCPs) derived from non-pathogenic Rhodotorula mucilaginosa to stimulate a Th17-biased response. The vaccine confers protection for both C57BL/6 and humanized HLA-DR4-transgenic mice against Coccidioides infection. In this study we have examined the essential pattern recognition receptors and immune adaptors that are required for the vaccine to induce a protective Th17 response.

Methods

We have explored the transcriptome landscape in bone marrow-derived macrophages (BMMs) exposed to the rCAP1+GCP vaccine using RNA sequencing (RNA-Seq) analysis. Control BMMs were incubated with culture medium alone. The RNA-Seq reads were aligned to the murine reference genome and analyzed using CLC Genomics Workbench, EdgeR and Ingenuity Pathway Analysis (IPA) software. Data were confirmed by quantitative real-time PCR analysis. Th17-type cytokines and Th17 cells in the Coccidioides-infected lungs were measured using ELISAs and intracellular cytokine staining flow cytometry. Knockout strains of mice that lack expression of Dectin-1, Dectin-2 and caspase recruitment domain-containing protein 9 (CARD9) were used for immune response and protective efficacy assays as we previously reported.

Results RNA-Seq data showed that 1,320 genes were differentially expressed in BMMs exposed to rCPA1+GCP compared to controls. Gene ontology and IPA analysis indicated that the up-regulated genes were related to antigen presentation, immune response and Th17 polarization, especially genes in the Dectin-1/Dectin-2-CARD9 pathway. All wild type C57BL/6 mice vaccinated with rCPA1+GCP mounted an early Th17 response and surivived for a period of 50 days postchallenge, while the vaccinated $CARD9^{-/-}$ mice significantly reduced the activation of Th17 cells and succumbed to coccidioidomcycosis. The vaccinated Dectin-$1^{-/-}$ and Dectin-$2^{-/-}$ mice also showed a signigicant increase of fungal burden in their lungs and spleen compared to the vaccinated C57BL/6 mice.

Conclusion

Taken together, our findings revealed that the newly created rCPA1+GCP vaccine engages the Dectin-1 and Dectin-2/CARD9 signal pathway to trigger a protective Th17 immune response against Coccidioides infection in this mouse model.

A CASE-CONTROL STUDY OF THE EFFECT OF SERTRALINE TREATMENT ON THE RISK OF DEVELOPING COCCIDIOIDOMYCOSIS

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Introduction

The antidepressant sertraline, a selective serotonin-reuptake inhibitor, has been demonstrated to have antifungal activity against Coccidioides in vitro. We hypothesized that persons on treatment with sertraline would have a decreased risk of developing coccidioidomycosis.

Methods

A case-control study was performed to determine the odds of developing coccidioidomycosis in persons treated vs. untreated with sertraline prior to onset of their infection. All cases of coccidioidomycosis, defined as a problem list entry and billing code for coccidioidomycosis, and receiving a prescription for fluconazole, from 1/1/2012-4/30/2017 were extracted from the electronic medical record at a referral hospital in Fresno, California. Matched controls were chosen from patients hospitalized with a diagnosis of non-fungal pneumonia, matched 3:1 to cases by age, sex, race, and ethnicity. Exposure to sertraline was defined as having an active prescription for sertraline at the time of diagnosis.

Results

Coccidioidomycosis was identified in 305 cases, and 915 matched control subjects were chosen at random. Sertraline was prescribed at time of diagnosis in 10 of the 305 cases (3.3%), and among 35 of the 915 controls (3.9%), giving an odds ratio of 0.81 ($p = 0.66$, 95% CI 0.4-1.7).

Conclusion

The odds ratio of 0.81 for developing Coccidioides infection on sertraline treatment is less than 1 suggestive of a possible protective effect of sertraline. However, this effect was not statistically significant. The lack of a significant reduction in Coccidioides infections with sertraline treatment could be due to including low dose sertraline treatment, which may not achieve an adequate tissue level to prevent infection. An attempt to analyze the subset of cases and controls on high dose sertraline was also not significant. However, this number of subjects was too low to have adequate statistical power to detect a difference (data not shown). Adherence to sertraline could not be assessed in this study, and adherence to antidepressant treatment has been reported to be as low as 40-50%. Low adherence to sertraline treatment would also lead our results to underestimate the potential effectiveness of sertraline at preventing Coccidioides infection.

THE NOVEL FUNGAL CYP51 INHIBITOR VT-1598 IS EFFICACIOUS IN A MURINE MODEL OF CNS COCCIDIOIDOMYCOSIS CAUSED BY *C. IMMITIS*

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Introduction Disseminated coccidioidomycosis can lead to significant morbidity, especially when this occurs in the CNS. In these patients, lifelong therapy is often required, with fluconazole being the drug of choice. However, this azole does not result in clearance of the organism from this site of infection. VT-1598 is a fungal-specific Cyp51 inhibitor that has demonstrated in vivo efficacy in murine models of pulmonary and CNS coccidioidomycosis caused by *Coccidioides posadasii*. Our objective was to evaluate the in vivo efficacy of VT-1598 in a murine model of CNS coccidioidomycosis caused by *Coccidioides immitis*.

Methods A contemporary clinical isolate of *C. immitis* collected from a CNS shunt and received by the Fungus Testing Laboratory for analysis was used. Species identity was confirmed by DNA sequence analysis. CNS infection was established in immunocompetent male ICR mice via intracranial inoculation with arthroconidia. Antifungal therapy began 48 hours post-inoculation and consisted of placebo control, VT-1598 (5 mg/kg, 15 mg/kg, and 45 mg/kg by oral gavage once daily), or fluconazole (25 mg/kg by oral gavage twice daily). Treatment continued for 7 and 14 days in the fungal burden and survival arms, respectively. Fungal burden was assessed by CFU counts in brain tissue collected one day after therapy stopped in the fungal burden arm, and on the days the mice succumbed to infection or on the pre-specified study endpoint in the survival arm (day 30, 15 days after therapy stopped). Differences in median survival and percent survival were analyzed by the log-rank test and chi-square test, respectively. Differences in fungal burden were assessed by the ANOVA with Tukey's post-test for normally distributed data, and by Kruskal-Wallis test with Dunn's post-test for non-normally distributed data.

Results Survival was significantly enhanced in mice treated with VT-1598 compared to placebo. Median survival was >30 days in each of the VT-1598 groups compared to 9 days for placebo ($p < 0.0001$). Fluconazole also significantly improved survival compared to placebo (29 days; $p < 0.0001$). Survival percentage was also significantly higher in the VT-1598 groups ($\geq$ 70%) compared to placebo (0%; $p \leq 0.0031$), while survival in the fluconazole group was 40%. In the fungal burden arm, each dose of VT-1598 (range of mean$\log_{10}$ CFU/g 1.43 - 1.80 for VT-1598) and fluconazole (mean $\log_{10}$ CFU/g 1.56) significantly reduced brain fungal burden compared to placebo (mean $\log_{10}$ CFU/g 5.77; $p < 0.0001$). In the survival arm, VT-1598 at 15 mg/kg and 45 mg/kg (median $\log_{10}$ CFU/g 1.40 and 1.42, respectively) also significantly reduced brain fungal burden compared to placebo (median $\log_{10}$ CFU/g 6.21; $p \leq 0.0018$). Fungal burden in these groups remained lower despite therapy being stopped 15 days before tissue collection. In contrast, fungal burden rebounded after therapy had stopped in the fluconazole group (median $\log_{10}$ CFU/g 6.10).

Conclusion VT-1598 was highly efficacious in this murine model of CNS coccidioidomycosis caused by *C. immitis*. Significant improvements in both survival and fungal burden were observed with VT-1598. Further studies are warranted to determine the clinical efficacy of VT-1598 in the treatment of CNS coccidioidomycosis.

FURTHER CHARACTERIZATION OF THE AVIRULENT ⌢CPS1 COCCIDIOIDES VACCINE IN MICE

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Introduction We previously presented data regarding the high level of protection from lethal infection afforded to C57BL/6 (B6) and BALB/c mice from the live avirulent ⌢cps1 vaccine. We showed 1) protection that lasts at least 6 months (B6 mice), 2) at least 6 months survival following lethal challenge with 40% of mice sterile at sacrifice (B6 mice), and maximal protection with a subcutaneous spore dose between 100,000 and 500,000 given twice (B6 and BALB/c mice). 10,000 spores given twice IN or SC predictably leads to very low fungal burdens after lethal challenge. Presented here, we verify a requirement for viability of the vaccine and further explore its fate in immunodeficient mice.

Methods C57BL/6 (B6) mice were vaccinated subcutaneously (SC) or intranasally (IN) with 10,000 spores of live, irradiated, or ethanol-killed spores of ⌢cps1 and challenged with a lethal dose of Coccidioides posadasii, strain Silveira, (WT) spores; lung fungal burden (LFB) was quantitated at 14 days post infection. B6 mice were vaccinated IN once or twice 2 weeks apart, challenged with WT 4 weeks later, and sacrificed for LFB at 14 days. B6 and BALB/c mice were immunosuppressed with cyclophosphamide (CTX) and given 10,000 or 100,000 spores of ⌢cps1 IN; mice were sacrificed for quantitative lung culture or histopathology 6 days after infection. $RAG1^{-/-}$ and B6 mice were given ⌢cps1 IN and challenged with WT for LFB at 2 weeks. Selected SC injection sites in various studies were analyzed by histopathology or quantitative culture as detailed in results. Statistical analysis was with ANOVA or T-test.

Results B6 mice vaccinated with either irradiated (>99.9% dead) or ethanol-killed spores had no reduction in lung fungal burden (mean ~Log6) as compared to saline controls, while those vaccinated with live ⌢cps1 had a mean 3.5 (SC) or 5 (IN) Log reduction in LFB compared to all other groups ($P<0.001$). B6 and BALB/c mice immunosuppressed with CTX and given up to 100,000 spores of ⌢cps1 IN exhibited lung ⌢cps1 fungal burdens ranging from none to 2.2×10^5 on day 6 p.i. In $RAG1^{-/-}$ and B6 mice vaccinated once intranasally and challenged with 60-65 spores WT, there was no demonstrable protection of RAG mice. However, a single IN vaccination also failed to protect B6 mice. We verified that RAG1-/- mice cannot be protected by either IN or SC vaccination, and also that two doses of ⌢cps1 IN or one SC reduce LFB while a single IN dose does not. ⌢cps1 persists in SC injection sites, though spherules and endospores appear atypical.

Conclusion A viable vaccine is required to induce protection with ⌢cps1. Additional studies to characterize the efficacy and safety of this vaccine have shown that the mutant strain persists in SC injection sites. The failure of a single vaccination IN to protect B6 mice when 2 vaccines protects very well suggests that at least temporary persistence of the mutant in tissues may be a requirement for immunity. Inability to protect with killed material supports this. Future studies to explore the relationship between mutant strain persistence and ongoing strong protection could be performed.

CUTANEOUS ADVERSE EFFECTS OF LONG-TERM FLUCONAZOLE USE IN COCCIDIOIDOMYCOSIS

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Introduction

Reversible alopecia, rash, dry skin, chapped lips, fixed drug eruptions, and severe cutaneous reactions have been briefly described, but not well defined, in patients on long-term fluconazole. Similar concerns are common in persons residing in the arid environment of Arizona, and it has not been clear whether the patient complaints were from desert life, symptoms of coccidioidomycosis, or adverse effects of fluconazole itself. The aim of this study was to define the severity of cutaneous adverse effects of long-term fluconazole treatment in this patient group.

Methods

A voluntary, one-time, survey was administered to patients diagnosed with probable or confirmed coccidioidomycosis who were either taking fluconazole > 1-month, or off fluconazole >1-month. Patients treated with other antifungals were excluded. In the survey, patients rated the severity of cutaneous symptoms (if any) within the last 30 days (1 = none, 2 = mild, 3 = moderate, 4 = severe). We compared the mean severity and prevalence of cutaneous symptoms in patients off fluconazole > 1-month (n=33) to patients with a > 1-month history of fluconazole use (n=60).

Results

Individuals with a > 1-month history of fluconazole use, when compared to those off fluconazole > 1-month, had more severe dry lips (3.0 vs 1.9, $P < .001$), dry mouth (2.4 vs 1.8, $P = .006$), dry skin (2.4 vs 2.0, $P = .047$), hair loss (2.0 vs 1.4, $P = .005$), and increased sweating (1.9 vs 1.5, $P = .049$). The prevalence of dry lips (96.7% vs 65.5%, $P < .001$) and alopecia (52.5% vs 24.2%, $P = .009$) was higher in the fluconazole group when compared to those off fluconazole. There was no significant difference in the severity of ocular symptoms, rash, pruritus, sun sensitivity, nosebleeds, hair texture, nail symptoms, acne, muscle aches, or dental problems.

Conclusion

Patient with coccidioidomycosis treated with fluconazole have more severe dry lips, dry mouth, dry skin, hair loss, and troublesome sweating than those without fluconazole. This finding helps practitioners to counsel coccidioidomycosis patients requiring fluconazole. Whether proactive or reactive use of products to alleviate such symptoms is beneficial for patients remains to be studied.

DELAYS IN DIAGNOSISING COCCIDIOIDOMYCOSIS WITHIN ITS ENDEMIC REGION

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Introduction

Diagnosis and therefore appropriate management of early Coccidioidomycosis (Valley Fever) depends on laboratory testing which if not specifically ordered can result in delays. If this interval were reduced, patients would be managed more precisely and unnecessary care, especially antibacterial treatments, could be eliminated. The purpose of this study is to determine the length of the delay from first seeking medical care to laboratory diagnosis of Coccidioidomycosis and to calculate total health care utilization during that period.

Methods

We selected charts within a 12 month interval for which ICD9 &10 codes for Coccidioidomycosis were first identified. Two physicians independently reviewed the EMR to exclude records with i) either mistaken coding, ii) prior coccidioidal infection that was missed in the initial selection, or iii) not confirmed by laboratory tests. For the remaining records, the date was identified of first medical evaluation of syndromes consistent with an illness subsequently determined to be Coccidioidomycosis. The eventual coccidioidal syndrome was categorized by type: 1) symptomatic pulmonary infection or related immunologic response (rash, arthralgia, fatigue); 2) extrapulmonary progressive infection; 3) fiborcavitary chronic pulmonary infection; 4) asymptomatic pulmonary nodules. We then calculated the time interval and applied a cost analysis to that interval.

Results

Of the first 86 charts, 41 charts (48%) were not excluded. Of these, a diagnostic delay ranged from 11-31 d in 29%, from 2-6 months in 27%. Same day diagnosis occurred in 5% and diagnosis was delayed more than 6 months in 18% after the initial presentation. Most patients presented with an acute pulmonary syndrome 63%. 12% had either disseminated disease or chronic fibrocavitary lesion, and approximately 14% had asymptomatic nodules.

Conclusion

We have demonstrated that more than half of the patients diagnosed with Coccidioidomycosis have a significant delay in diagnosis (2 weeks to 6 months). This creates the opportunity for toxicity and drug resistance from unneeded antibacterial use and for accumulated expenses of misdirected medical care prior to the correct diagnosis. We hope that the results from this study and future studies provide the basis for effective interventions to reduce the interval in diagnosis of Valley Fever.

ANTI-COCCIDIOIDAL COMPLEMENT FIXING ANTIBODIES ARE SPECIFIC FOR A NEWLY IDENTIFIED TRUNCATION OF THE CTS1 GENE PRODUCT

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Introduction

The detection of anti-coccidioidal complement fixing (CF) antibodies in serum, cerebrospinal fluid, and other bodily fluids has been the basis for highly specific diagnostic tests and its quantitation has prognostic value. Past studies from three independent laboratories have identified the chitinase enzyme, expressed from *cts1*, as the 427 amino acid (a.a.) protein (Cts1) which CF antibodies recognize. In a previous analysis (Yang et al., 1997), an a.a.20-310 truncation bound CF serum antibodies from patients with coccidioidomycosis but did not cross react with serum from patients with either histoplasmosis or blastomycosis. We have now identified that CF antibody binding can be further localized to a.a.111-310.

Methods

Amplimers of the full-length *cts1* and truncations encoding a.a.20-310 and a.a.111-310 were generated by PCR with DNA encoding a poly-His sequence added to the 3' end. Amplimers were cloned into pMCSG7 for transfection into *E. coli* BL21(DE_3) for expression. Recombinant peptides were extracted with 7M urea, and preliminary purification was accomplished by affinity binding to a nickel-NTA column. Following renaturation, proteins were analyzed by PAGE and subsequent immunoblotting.

Results

Immunoblots demonstrated that both the a.a.20-310 and the a.a.111-310 recombinant peptides reacted to sera from patients with coccidioidomycosis that contained CF antibodies but did not react with sera from uninfected patients. Absorption of CF positive sera with a.a.111-310 eliminated immunoblot binding of the sera to a.a.20-310. In other studies, similar expression was carried out in *Saccharomyces* but unacceptable background resulted from antibodies in serum from uninfected persons, presumably as the result of protein glycosylation.

Conclusion

We have discovered that a peptide of Cts1 which is 31% smaller than that previously reported retains affinity for all CF antibodies. Further studies are planned to examine still smaller truncations to identify the smallest truncation responsible for near all of CF binding. We hope that the results from these and future studies may provide the basis for a reference enzyme-linked immunoassay to mimic quantitative results currently produced by the originally described CF antibody detection assay.

COCCIDIOIDOMYCOSIS IN ALPACAS

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Introduction

The disease expression of *Coccidioides* fungi varies among different animal species. Llamas and alpacas (New World camelids) appear to be susceptible to wide-spread, severe disease with a high mortality. There is little published literature on either species, but regarding alpacas specifically, there is a single report of fulminant disease in a dam and aborted fetus. The objective of this research was to determine the impact of coccidioidomycosis in alpacas.

Methods

An anonymous, web-based survey was distributed to alpaca owners in endemic regions. Respondents were asked to report on the number of their alpacas diagnosed with coccidioidomycosis between 2005 and 2016. Owners with diagnosed animals were then asked to report on the diagnosis, treatment, and outcome for each ill animal. Secondarily, necropsy records of coccidioidomycosis in alpacas from the University of Arizona Veterinary Diagnostic Laboratory (AZVDL) were reviewed and manifestations of disease tabulated.

Results

Nearly 5% of the alpacas reported in the survey had been diagnosed with coccidioidomycosis. Alpacas residing in counties of Arizona with a high incidence of human coccidioidomycosis were found to have a 5.8 times greater risk of developing disease compared to alpacas residing in other areas of Arizona. Most alpacas were diagnosed by positive anticoccidioidal antibody serology, although five owners reported that the diagnosis was made upon necropsy. Reported clinical signs were often nonspecific and related to general loss of condition. Some animals experienced sudden death with no clinical signs. Ninety-two percent of untreated alpacas died, while owners reported 50% of animals treated with an azole antifungal survived. Overall mortality of alpacas with coccidioidmycosis was 78%. AZVDL necropsy records from 2007-2016 revealed 10 alpacas with *Coccidioides* spherules identified in tissues and nine of those had extensive disease in lungs, thoracic lymph nodes, and multiple other organs, directly causing death. Granulomas with spherules were found in the heart and/or pericardium in 5 of the 9 alpacas.

Conclusion

Alpacas in endemic regions are at risk of developing coccidioidomycosis that has a high fatality rate. Specific antifungal treatment was only 50% successful and failure to treat was almost universally fatal. Necropsy findings included extensive lung disease and widespread dissemination to other organs. The 56% rate of cardiac infection was higher than reported in other animals or humans. Failure of azole treatment may be related to drug absorption since literature shows these animals do not absorb oral voriconazole efficiently. Pharmacokinetic studies of fluconazole to determine doses that produce therapeutic blood levels might improve treatment outcomes. Raising awareness and engaging in research to better understand coccidioidomycosis in alpacas may prevent deaths.

STRESSED OUT: A CASE OF ADRENAL INSUFFICIENCY AND SEPTIC SHOCK IN COCCIDIOIDOMYCOSIS

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Introduction

Coccidioidomycosis is a commonly encountered disease in Northern California, however septic shock is an unusual presentation. We present a case of a 34 year old immunocompetent man with a history of disseminated Coccidioidomycosis, noncompliant with prior Posaconazole regimen in 2015, presenting with a two month history shortness of breath and cough.

Case Findings

Our patient first presented with neck and abdominal cutaneous lesions in 2013, and partially completed a course of Fluconazole at that time. He was later admitted in August 2014 with dysphagia, and was found to have retropharyngeal and mediastinal abscesses culture positive for Coccidioidomycosis. Additionally, he was found to have multiple cranial lesions. He was started on Amphotericin, developed renal failure and was transitioned to Posaconazole, however did not finish the treatment course upon discharge. He presented in August 2016 with two months of dyspnea, weight loss, decreased appetite, cough, and two actively draining R axillary lesions. On admission, he was febrile, tachypneic, hypoxic to 73%, with a leukocytosis and chest x ray concerning for bilateral diffuse reticulonodular opacities, consistent with disseminated Coccidioidomycosis.

Clinical Course

He was started on liposomal Amphotericin, and Vancomycin/Levoquin for broad spectrum coverage. The day after admission, he was intubated for worsening hypoxia and increased work of breathing, additionally requiring Levophed for pressure support. His clinical condition continued to worsen, with evidence of ARDS on imaging, renal failure requiring dialysis, and worsening hemodynamics requiring maximum pressor support. A cortisol stimulation test revealed adrenal insufficiency, and Hydrocortisone 100mg q8 was started.

Outcome

After starting Hydrocortisone, his clinical condition improved over the next two weeks, with decreasing pressor requirements, improved respiratory status, and decreasing sedation requirements. Axillary lesion cultures grew Coccidioidomycosis with positive serum Cocci IgM and IgG complement fixation studies. Unfortunately, during his recovery, the patient developed aspiration pneumonia and ultimately passed away three weeks after admission.

Conclusion

This case is a rare presentation of septic shock due to Coccidioidomycosis in an immunocompetent patient, a condition now uncommonly encountered given effective therapeutics in the setting of medication compliance. Though Coccidioidomycosis is not typically associated with adrenal involvement, there are autopsy reports from older pathology studies to indicate granulomatous involvement of the adrenal glands in disseminated Coccidioidomycosis. Thus it is important to consider adrenal insufficiency as a rare, but possible, contributing factor to shock in these patients, and to consider timely corticosteroid therapy.

COCCIDIOIDOMYCOSIS IN THE VETERANS HEALTH ADMINISTRATION (VHA), 2010-2017

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Introduction

The incidence of coccidioidomycosis (CM) has increased in recent years, but there is little data about CM in Veterans. Herein, we describe the epidemiology of CM in VHA during 2010-2017.

Methods

CM-coded hospitalizations and outpatient visits, as well as *Coccidioides* culture results were obtained from VHA's Praedico Public Health Surveillance System (1/1/2010-5/17/2017). Data extracted included patient demographics, location, diagnosis codes, encounter details and deaths during CM-coded hospitalizations.

Results

A total of 4,523 unique patients were identified. Of these, 28 were identified by culture result only and had no CM-coded encounters during this time period. Median age was 63 years (range 20-95), and 93% (4,228) were male. Over 76% (3,447) resided in the West US Census region, with the top counties of residence being Maricopa, AZ (769), Pima, AZ (712), Los Angeles, CA (242), Pinal, AZ (159), and Kern, CA (113). For 1,916 recorded hospitalizations (1,202 unique individuals, 27% of total cohort), median stay was 5 days, with 318 (17%) including time in intensive care and 89 deaths (5%). CM was the principal diagnosis for 342 (18%) of the hospitalizations. Race data were available for hospitalized patients, with 66% White, 23% Black/African-American, 2% American Indian/Alaska Native, and 2% Asian or Pacific Islander (8% missing). Hispanic/Latino ethnicity was recorded in 9%. There were 24,415 CM outpatient visits (3,982 unique individuals, 88% of total cohort). Hospitalizations and outpatient visits for 2010-2016 ranged from 242-288 admissions and 2,969-3,641 outpatient visits annually. Types of CM recorded and select comorbidities are presented in Table 1.

Conclusion

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

Table 1. Veterans Health Administration Coccidioidomycosis (CM) Encounter Details, 2010-2017

	Hospitalizations N=1916	Unique Inpatients[†] N=1202	Outpatient Visits N=24415	Unique Outpatients[†] N=3982
Types of CM, N (%)[‡]				
Pulmonary[§]	901 (47)	552 (46)	8682 (36)	1584 (40)
Primary pulmonary	311 (16)	232 (19)	3264 (13)	627 (16)
Other forms of progressive	262 (14)	129 (11)	2259 (9)	141 (4)
Meningitis	137 (7)	50 (4)	1369 (6)	77 (2)
Primary extrapulmonary	25 (1)	18 (1)	464 (2)	93 (2)
Unspecified	635 (33)	479 (21)	12052 (49)	2125 (53)
Select comorbidities, N (%)[‡]				
Diabetes Mellitus	666 (35)	392 (33)	2730 (11)	454 (11)
COPD	367 (19)	223 (19)	1587 (7)	335 (8)
Malignant Neoplasm	242 (13)	163 (14)	1092 (4)	231 (6)
HIV/AIDS	67 (3)	34 (3)	721 (3)	84 (2)
Transplant	59 (3)	19 (2)	296 (1)	25 (0.6)
Inflammatory Bowel Dx	29 (2)	18 (1)	108 (0.4)	16 (0.4)

[†]Based on the first CM-coded hospitalization record or outpatient encounter.
[‡]Based on ICD-9/ICD-10-CM diagnoses for the CM-coded encounter. Outpatient visits include up to 25 codes. Hospitalizations include a principal discharge and up to 25 secondary codes. Codes are not mutually exclusive. [§]Includes primary pulmonary, chronic pulmonary or pulmonary unspecified CM.

PATIENT WITH 40 YEAR HISTORY OF COCCIDIOIDAL MENINGITIS

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Introduction

Meningitis is the most feared form of disseminated extrapulmonary coccidioidomycosis, which is caused by fungal species *Coccidioides immitis* or *Coccidioides posadasii*. According to the 2016 IDSA Clinical Practice Guideline for the Treatment of Coccidioidomycosis, the treatment of choice is 400 mg oral fluconazole daily. If this clinically fails, options are to gradually increase fluconazole to a maximum of 1200 mg, to change to another azole or to initiate intrathecal Amphotericin B therapy. For the most common complication, hydrocephalus, a shunt for decompression is nearly always required. Duration of therapy is considered to be indefinite, as re-occurrence after presumed cure has been reported. Presented here is an active case of coccidioidal meningitis whose treatment has been continuous for 40 years.

Case findings

54 year old Caucasian male was initially diagnosed with central nervous system coccidioidomycosis at age 14. Past medical history include cranial nerve VIII damage related to amphotericin toxicity, neurogenic bladder and erectile dysfunction secondary to lumbar arachnoiditis, hypokalemic paralysis related to fluconazole therapy, seizure disorder diagnosed at age 4 and treated with Dilantin for 30 years, coronary artery disease with two myocardial infarctions (MI) and drug-eluting stent placement in January 2016, hypertension, hyperlipidemia, and hydrocephalus. Past surgical history include ventriculoperitoneal (VP) shunt placement at age 33 with 2 additional revisions. Current medications include fluconazole 1200mg daily, lisinopril, metoprolol, aspirin, clopidogrel, ezetimibe, and anti-PCSK9 monoclonal antibody bimonthly injections. Highest education level achieved is high school.

Clinical Course

Patient received intrathecal amphotericin B deoxycholate from age 14 to 29 via ventricular cistern. Cranial nerve VIII was gradually damaged during this time. When azoles became available in the early 1980s, patient was started on fluconazole 400mg. This was gradually increased to 1200mg over the next decade as CSF cultures continued to be positive. Mild hydrocephalus was initially detected at age 29. Hydrocephalus worsened and by age 33, a VP shunt was required. Nuclear bone scans and full body x-rays have not detected other sites of disseminated extrapulmonary coccidioidomycosis.

Outcome

Patient has been clinically stable for more than a year. There has been good follow up at outpatient clinics. Patient has been adherent to fluconazole therapy to this day. Most recent serum serology revealed IgG reactivity with 1:8 compliment fixation levels. CSF serology revealed weak reactivity to IgG at 1:1 compliment fixation level.

Conclusion

To our knowledge, this is the longest surviving patient with central nervous system coccidioidomycosis. The need for indefinite azole suppressive therapy is demonstrated here.

CRESENDO TRANSIENT ISCHEMIC ATTACKS DUE TO BASILAR COCCIDIOIDAL MENINGITIS WITH COCCIDIOMA

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Introduction

Meningitis is the most feared form of disseminated extrapulmonary coccidioidomycosis, which is caused by the fungal species *Coccidioides immitis* or *Coccidioides posadasii*. The most common presenting symptom is headache. Other symptoms include altered mental status, with or without fever, personality changes, nausea, vomiting, meningismus, gait abnormalities and focal neurological deficits. Presented here is a case of coccidioidal meningitis that initially presented as multiple consecutive crescendo transient ischemic attacks (TIA).

Case findings

64 year old Hispanic male with diagnosis of pulmonary coccidioidomycosis whom his treatment was stopped by outside physician presents with two episodes of headache, left-sided weakness and right facial droop, each episode more severe than the last but resolved in five minutes. This was preceded by two weeks of daily headaches and a year of blurry vision.

Clinical Course

In the emergency department, while having vitals taken, patient had another episode of right facial droop and left-sided weakness that resolved in five minutes. Stroke protocol was activated. Emergent computed tomography (CT) of brain without contrast as well as angiography of brain were unremarkable. However, later that evening, patient had another episode of right facial droop and left-sided weakness, followed by new onset slurring of speech, resolving in five minutes. Magnetic resonance imaging (MRI) of brain showed no infarcts or intracranial hemorrhage. However, there was increased peripontine enhancement, with nodular enhancement in the left peripontine area suspicious for basilar coccidioma. CSF analysis showed elevated protein and compliment fixation levels of 1:4 consistent with coccidioidal meningitis. Serum serology revealed IgG reactivity at 1:4 and IgM very weak reactivity.

Outcome

Patient had a total of 4 crescendo TIAs. He was placed on fluconazole 1000 mg daily and dexamethasone taper. Patient was discharged to be followed up in clinic. Unfortunately, one month later, patient had another episode of "Fall" at home with residual weakness and positive orthostatics was admitted and found to have lumbar compression fracture of L1 vertebra without radiographic evidence of osseous dissemination of coccidioidomycosis.

Conclusion

To our knowledge, this is the first report case of crescendo TIAs as the presenting manifestation of coccidioidal meningitis.

COCCIDIOIDOMYCOSIS: IT'S ALL IN THE LABORATORY RESULT—A CHANGE IN SURVEILLANCE PROCEDURE

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Introduction

Between 2011 and 2016, the number of coccidioidomycosis cases reported to the Los Angeles County (LAC) Department of Public Health (DPH) increased from 340 in 2011 to 901 in 2016 (+165%). As the case definition required both a positive laboratory test and compatible symptoms/signs, DPH's time and resources used reviewing case records increased substantially. We analyzed reported cases from 2011-16 to assess positive predictive value of laboratory results alone to define a coccidioidomycosis case. We also analyzed the cases to assess the positive predictive value (PPV) of enzyme immunoassay (EIA) alone.

Methods

We included all cases reported to LAC DPH between January 2011 and August 2016. We followed the Council of State and Territorial Epidemiologists (CSTE) definition, which laboratory criteria includes detection of coccidioidal immunoglobulin M (IgM) by immunodiffusion, EIA, latex agglutination, or tube precipitin; or detection of coccidioidal immunoglobulin G (IgG) by immunodiffusion, EIA, or complement fixation. For reported cases that did not meet the CSTE definition, we identified the reason, including absence of clinical symptoms in the context of a positive laboratory test. Positive predictive value of laboratory criteria alone were calculated. Positive predictive value of EIA alone were calculated.

Results

We identified 5,820 case reports during the study period. Of these 3,157 reports, cases were excluded due to residence outside of LAC, duplicate of a prior confirmed report, or absence of documented clinical criteria. Medical records were available for review of 2,663 reported cases. Overall, symptoms consistent with coccidioidomycosis were identified for 2,583. Eighty (80) cases had no documented clinical signs/symptoms. Thus, the PPV of using laboratory criteria alone without clinical findings to define a case was 97%. We analyzed 4113 laboratory reports. Of those, 96 reports were tested by EIA alone, and two had no documented compatible signs/symptoms. PPV for EIA alone was also 97%.

Conclusion

Based on our analysis, we revised our surveillance procedure to require only laboratory criteria to confirm a coccidioidomycosis case. Eliminating the need to review clinical criteria frees substantial time that now can be focused on outreach and prevention activities.

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

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INTRODUCTION

Patients who are treated with inhibitors of tumor necrosis factor (TNFI) sustain deficiencies of cellular immunity, and may acquire life-threatening mycobacterial and fungal infections. Coccidioidomycosis can be severe, disseminated or fatal in recipients of TNFI. Whereas multiple specialty society guidelines recommend screening for and treatment of latent tuberculosis prior to institution of TNFI therapy, there is no published data assessing the efficacy of screening for asymptomatic coccidioidomycosis. The medical providers in our multispecialty practice located in the *Coccidioides*-endemic region commonly screen for tuberculosis, coccidioidomycosis, and other pathogens prior to institution of TNFI. The objective of this study was to assess the utility of screening for coccidioidomycosis in this population.

METHODS

We performed an electronic search of all patients prescribed infliximab, etanercept, adalimumab, certolizumab or golimumab for rheumatologic, inflammatory bowel, or dermatologic conditions, who also had testing for coccidioidomycosis from 4/4/2010 to 9/26/2016. From that list, we selected and reviewed patients who had positive coccidioidal serologies performed for screening purposes.

RESULTS

1036 patients on TNFI had coccidioidal serologies performed. Of these, 982/1036 (95%) patients met our inclusion criteria. Of these, 883/982 (90%) were seronegative and 99/982 (10%) were seropositive for coccidioidomycosis. 52/99 (53%) of the seropositive patients were found through screening: 34/52 (65%) diagnosed from baseline (pre-TNFI) screening and 18/52 (35%) diagnosed based on annual screens. 47/99 (47%) of the seropositive patients were diagnosed not by screening, but rather when patients presented for new symptoms. In terms of the specialties these 52 patients were screened by: Gastroenterology (30/52, 58%), Rheumatology (15/52, 29%), and Dermatology (7/52, 13%). After identifying the positive coccidioidal serology, 39/52 (75%) of these patients were evaluated formally by Infectious Diseases. Of the 18/52 (35%) diagnosed based on annual screens, 9/18 (50%) patients had their TNFI therapy stopped. Of the 34/52 (65%) diagnosed from baseline screening, 5/34 (15%) were not initiated on TNFI treatment. 17/99 (17%) seropositive patients were positive for EIA IgM-only, and 14/17 (86%) were not treated with an antifungal. All had TNFI instituted without active coccidioidomycosis in follow-up.

CONCLUSION

Both baseline and annual screening identified patients with positive serology, implying the presence of active disease that may not have been discovered had screening not been performed.

PRELIMINARY ESTIMATES OF ANNUAL BURDEN OF COCCIDIOIDOMYCOSIS IN THE UNITED STATES, 2010-2014

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Introduction Approximately 10,000 coccidioidomycosis cases are reported in the United States each year. However, the true number of cases is substantially higher because some infected persons do not seek medical care, patients are misdiagnosed, and some identified cases are not reported to public health. An estimate of the true number of cases is needed to increase public and healthcare provider awareness and to inform public health and policy decision-making.
Methods To estimate yearly incident symptomatic coccidioidomycosis nationwide during 2010–2014, we combined estimates from six multi-stage multiplicative models using seven independent data sources: (1) US Census data, (2) county-level coccidioidin skin test reactivity data from the 1950s, (3) National Notifiable Disease Surveillance System (NNDSS) data, (4) Healthcare Cost and Utilization Project (HCUP) data, (5) Veterans Health Administration data, (6) the Truven Health MarketScan® Research Databases, and (7) Multiple Cause of Death data. One model estimated incident symptomatic coccidioidomycosis cases by multiplying Census data by county-level skin test negativity to determine the population at risk, multiplied by an annual infection rate, which was estimated based on skin test and NNDSS data (adjusted for under-diagnosis and under-reporting). The five remaining models scaled up coccidioidomycosis-specific data on mortality, hospitalizations, meningitis-related hospitalizations, and inpatient and outpatient health insurance claims. We used beta-PERT distribution as our basic probability distribution describing plausible values of each of the model components (minimum, maximum, mode value, and a parameter that controls the spread of the distribution). We used Monte Carlo sampling to estimate the yearly number of incident symptomatic cases for each model, with model parameters drawn from an appropriate beta-PERT distribution (defined by minimum, maximum, mode and scale parameters). Model outputs are represented as mean point estimates with 95% credible intervals (CIs). We obtained an overall estimate of yearly incidence by constructing a sample distribution of sample means of the combined models; similarly we are able to obtain upper and lower CIs of this estimate. We used Microsoft Excel, SAS, and R for analysis.
Results Our preliminary estimates suggest that yearly incident symptomatic coccidioidomycosis cases ranged from 131,541 (95% CI: 69,472–193,611) in 2010 to 115,859 (58,367–173,738) in 2014, with a peak in 2011 of 145,576 (76,737–214,813) cases.
Conclusion The annual burden of symptomatic coccidioidomycosis in the United States is likely 6 to 14 times higher than the number of reported cases. Improved awareness, laboratory diagnosis, medical coding, and reporting to public health are needed.

PEDIATRIC CENTRAL NERVOUS SYSTEM COCCIDIOIDOMYCOSIS: A CASE SERIES

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Introduction

Central nervous system (CNS) coccidioidomycosis is associated with high morbidity and mortality, but clinical data are sparse especially in the pediatric population due to rarity of this condition. We present four pediatric patients with CNS coccidioidomycosis managed at a quaternary center between 2010 and 2016.

Case findings

Age at presentation varied between 3 and 18 years; two males and two females. Reported races/ethnicities were Hispanic (2), Filipino (1) and Caucasian (1). All patients lived in the California Central Valley; none of them was known to be immunocompromised. The diagnosis was established by positive coccidioides antibody immunodiffusion in the cerebrospinal fluid. Time from onset of symptoms to diagnosis ranged from 3 weeks to 4 months; all patients were initially diagnosed and treated for upper respiratory infections or chronic sinusitis. Onset of symptoms was between November and February in all patients. Three had radiologic findings suggestive of vasculitis and CNS infarcts.

Outcome

Two patients developed neurologic deficits; one had multiple motor and linguistic deficits with near complete recovery and the other had gradual progression to persistent vegetative state and died. Both patients received corticosteroids of different doses and duration. The patient who died had bilateral multifocal beading and irregularities of anterior and posterior cerebral circulations on MR angiography. The other two patients have intermittent symptoms of headache, malaise and in one patient, back pain and vomiting, despite ongoing antifungal therapy.

Conclusion

In our case series of CNS coccidioidomycosis, the patients presented with symptoms of upper respiratory infection in winter months, likely delaying diagnosis and management of coccidioidomycosis. This highlights the importance of educating community physicians in endemic areas to have a high index of suspicion in cases of protracted sinusitis that is unresponsive to therapy, or those associated with prolonged fever, persistent headache or significant malaise. In comparison, the patient who died had significant abnormal imaging of intracranial vasculature suggestive of severe vasculitis and received higher doses of corticosteroids for a longer duration.

EVALUATION OF THE VALLEYFEVERDx (IMMY), A RAPID LATERAL FLOW ASSAY FOR THE DETECTION OF ANTI-*COCCIDIOIDES* IgG AND IgM ANTIBODIES

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Introduction

Coccidioidomycosis (Valley Fever) is an invasive fungal infection endemic to the southwestern United States, Mexico, and South America. Valley Fever causes disease symptoms similar to those of other common illnesses creating a delay in correct diagnosis. Further delaying an accurate diagnosis is the use of time-consuming diagnostic assays that must be performed in reference laboratories. These assays frequently involve complex techniques performed by highly trained technicians using non-standardized protocols. A rapid and simple test is needed for the diagnosis of Valley Fever. We developed the ValleyFeverDx (IMMY) lateral flow assay (LFA) capable of distinguishing anti-*Coccidioides* IgG and IgM antibodies in patient serum in twenty minutes.

Methods

We characterized 169 serum specimens as proven, probable, or negative for disease using complement fixation, immunodiffusion, and EIA assays. Serum specimens were diluted in lateral flow specimen diluent. 100uL of each diluted specimen was added to the anti-*Coccidioides* IgG and the anti-*Coccidioides* IgM LFA and incubated at room temperature for 20 minutes. Positive LFA results were detected by the presence of a control and a test line. Negative LFA results were detected by the presence of a control line only. Completed LFA's were read independently by two operators and ROC analysis was performed to determine overall assay sensitivity and specificity.

Results

We tested the ValleyFeverDx LFA using serum specimens characterized as proven, probable, or negative for disease. When compared to current reference laboratory testing methods the estimated area under the ROC curve was found to be 0.96 (95% CI = [0.92, 0.98], standard error = 0.01, $p<0.0001$). The ValleyFeverDx LFA had a sensitivity of 97.63% (95% CI = [94.0, 99.3]) and a specificity of 93.44% (95% CI = [84.0, 98.1]).

Conclusion

The ValleyFeverDx is a rapid, simple, and highly sensitive lateral flow assay for the detection of anti-*Coccidioides* IgG and IgM antibodies. This simple LFA is lower in complexity than current testing methods. Furthermore, the decrease in time-to-results and detection of anti-*Coccidioides* IgG and IgM antibodies makes the ValleyFeverDx a near patient diagnostic test that could significantly reduce the delay in Valley Fever diagnosis.

IMPROVED SENSITIVITY FOR DETECTION OF COCCIDIOIDOMYCOSIS IN DOGS WITH COMBINED ANTIBODY AND ANTIGEN TESTING

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Introduction

Although the definitive diagnosis of coccidioidomycosis (CM) in dogs is based on identification of the organism by cytology, histology or culture, this is often difficult to achieve. Serology by agar gel immunodiffusion (AGID) for reactivity to the CF and TP antigens is often employed, although this may be falsely negative in patients with immunocompromise or acute disease. The use of an antibody enzyme immunoassay (EIA) and antigen detection test may improve overall sensitivity.

Methods

Serum from 21 dogs with pathology-proven CM was tested for *Coccidioides* antibody by AGID and the MVista canine IgG EIA. Serum and urine were tested in the MVista *Coccidioides* antigen EIA. Control dogs from Arizona were also assessed, including 32 healthy dogs and 16 dogs with nonfungal pulmonary disease.

Results

Of dogs with proven CM, AGID was positive for CF antigen in 16/21 (76.1%), although titer was ≥ 1:4 in only 14/21 (66.7%). IgG was positive in 18/21 CM dogs (85.7%; p=0.125 compared to AGID **≥1:4**). Antigen was detected in urine or serum in only 9/21 (42.9%) CM dogs. IgG or antigen was detected in 20/21 (95.3%), and AGID, IgG or antigen were positive in all dogs (100%). Combined IgG and antigen testing, or testing all 3 methods improved sensitivity over AGID **≥1:4 only; p<0.05.** Specificity in healthy dogs was 90.6% (29/32) for either AGID or antibody EIA, and 100% for antigen test. Specificity for all tests was 100% for clinical control dogs.

Conclusion

Compared to AGID, MVista canine IgG EIA was positive in a higher percentage of dogs with proven CM; however, statistical significance could not be achieved due to low study numbers. Antigen testing has low sensitivity overall; however, some dogs with CM lack detectable antibody, but have positive antigen. In order to achieve the highest sensitivity for diagnosis of CM, assessment of both antibody and antigen is recommended. Some cases may require antibody testing by both EIA and AGID.

RAPID DETECTION OF ANTI-*COCCIDIOIDES* ANTIBODIES USING THE sona ™ *COCCIDIOIDES* AB LATERAL FLOW ASSAY (IMMY)

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Introduction

Coccidioides, the causative agent of San Joaquin Valley Fever, is a fungal agent endemic to the arid regions of the Americas. Due to the difficulties associated with fungal culture, the dominant method of diagnosis is serology. Coccidioidomycosis serology can be a laborious, time consuming and expensive process. It is for this reason that many hospitals rely on send out diagnostic testing from reference laboratories. IMMY has developed a lateral flow assay designed to quickly rule out negative cases, near the point of care. Reduced turnaround time, cost-savings and enhanced anti-microbial stewardship are benefits of the assay, in addition to those provided by more rapid patient management. The IMMY sona™ *Coccidioides* Ab lateral flow could be an effective tool for ruling out potential *Coccidioides* infections.

Methods

Ninety-two patient samples were characterized by the University of California, Davis Coccidioidomycosis Serology Laboratory and IMMY. Specimens were considered positive if reactive in two of any of the regularly performed assays: complement fixation, immunodiffusion or quantitative immunodiffusion (performed at UC-Davis) and Premier® Coccidioides EIA manufactured by Meridian Bioscience (performed at IMMY). These specimens were kindly provided to IMMY for the evaluation of a new lateral flow assay designed to quickly rule out negative cases. Briefly, specimens were diluted to 1:441 in specimen diluent, run on the assay for a total of 20 minutes and independently read by two operators. An ROC curve analysis was performed to determine assay sensitivity and specificity.

Results

The area under the ROC curve was 0.885 (95% confidence interval (CI) = [0.801,0.942], standard error 0.0377, $p<0.001$) for the sona™ *Coccidioides* AB assay. The assay had 100% sensitivity 95% CI = [91.1, 100] and 76.92% specificity 95% CI = [63.2, 87.5] when compared to the reference method. The positive predictive value was 76.92% and the negative predictive value was 100%.

Conclusion

The sona™ *Coccidioides* Ab test is a rapid immunoassay that detects both anti-*Coccidioides* IgG and IgM antibodies. The high negative predictive value of the assay allows for a 20 minute screen to rule out patients suspected of having Valley Fever. Management of this population of patients can be significantly improved by ruling out Valley Fever, allowing physicians to better direct treatment. Patients positive on the sona™ *Coccidioides* AB test can then be referred to more traditional serology techniques to confirm the presence of antibodies to *Coccidioides*.

DETERMINING MECHANISMS OF PROTECTION IN A LIVE ATTENUATED COCCIDIODES VACCINE

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Introduction

Coccidioidomycosis, caused by the two species *Coccidioides immitis* and *C. posadasii*, is an endemic disease in northern Mexico and the southwestern United States. Our goal is to develop an effective vaccine. Previous work in our laboratory has shown that vaccination with a live attenuated mutant Δ*cps1* can protect mice from a lethal intranasal *Coccidioides* challenge. This protection is durable, lasting at least six months post vaccination, and effective regardless of the vaccination route (intranasal, subcutaneous, intraperitoneal). Here we dissect the mechanisms of protection using cellular transfers into naïve mice.

Methods

C57BL/6J (B6) mice were vaccinated twice subcutaneously with 50,000 spores of Δ*cps1* 2 weeks apart. Ten days after boosting mice were sacrificed and spleens and serum were harvested. Spleen cells for transfer were fractionated using negative selection. Serum or fractionated spleen cells were transferred to naïve mice intraperitoneally. The following day mice were challenged with a lethal intranasal dose of *C. posadasii*, strain Silveira, spores. Mice were sacrificed at 14 days post challenge for lung fungal burden quantitation.

Results

Transfers of splenocytes, but not serum from vaccinated animals resulted in a significantly reduced fungal burden compared to unvaccinated cellular transfers. Flow cytometric analysis indicated that vaccination produces antigen specific $CD4^+$ IFN-γ^+ T cells. Further cellular fractionation showed than splenocytes depleted of T cells had no protective effect; conversely, transfer of $CD4^+$ cells showed a similar effect to whole spleen transfers.

Conclusion

$CD4^+$, but not $CD8^+$, cellular transfer can reduce fungal burdens after lethal *C. posadasii* challenge. The fact that transfer of serum had no effect indicates the humoral immune response was not responsible for the protective effect imparted by Δ*cps1* vaccination. Further work is being carried out to determine the direct effect of the $CD4^+$ cells on *Coccidioides* challenge.

OCCUPATIONAL AND RECREATIONAL DUST EXPOSURES IN MARICOPA COUNTY RESIDENTS WITH COCCIDIOIDOMYCOSIS

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Introduction

In Maricopa County, Arizona, Coccidioidomycosis ("cocci") is one of the most frequently reported infectious diseases. Due to the temperate climate and long-outdoor season, a vast majority of the population enjoys various outdoor recreational activities. In order to explore risk factors, the Maricopa County Department of Public Health (MCDPH) is undertaking a 12-month study to collect occupational and recreational information.

Methods

A case-series study with 300 laboratory-confirmed cocci cases is being conducted. Participants include those ≥18 years of age with recent laboratory evidence of infection and at least one phone number reported.

Results

Study is still in progress, all presented data is preliminary. From October 1, 2016 – June 30, 2017, MCDPH investigators interviewed 205 (7.4%) of the 2788 reported cases during this time period. The median age of interviewed cases was 59 (range 19 – 89) years and just over half were female (54%). The majority of interviewed cases self-identified as white, non-Hispanic (84%).
Seventy-five percent of cases reported working in the past year; 25% worked either outside or both inside and outside. Only 15% stated they disturbed soil while working. Almost 90% of cases interviewed were symptomatic. Symptomatic individuals participated in a median of 2 outdoor activities (range 0-7) and spent a median of 10 hours outdoors (range 0-100) in the month prior to their illness onset. Frequent activities reported included: walking outside (63%), gardening (36%), and hiking (33%); however, 14% did not participate in any outdoor activities.
Diagnosis status was assessed for all interviewed cases. Symptomatic cases who had both an EIA IgM and IgG positive result were 10 times more likely to be diagnosed with cocci than were symptomatic cases with just an EIA IgG positive result.

Conclusion

Our results demonstrate that the majority of our cases spend considerable time outdoors, regardless of age. Continued, routine interviews may provide information to help determine which outdoor activities put individuals at a higher risk for developing cocci, however a control group with outdoor exposure history is needed to determine relative risk. Based on the number of cases with an isolated positive IgG for and no physician diagnosis of coccidioidomycosis, provider education is needed to train healthcare providers regarding the interpretation of coccidioidomycosis serology results.

ANALYSIS OF SERUM CHITINASE ACTIVITY IN INDIVIDUALS WITH PULMONARY AND EXTRAPULMONARY COCCIDIOIDOMYCOSIS

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Introduction

Both prospective and retrospective studies have indicated that dissemination of coccidioidomycosis occurs at an elevated rate among otherwise healthy African Americans and Filipinos, suggesting genetic predisposing factors may be present. In a previous study, we performed whole exome sequence analysis of 22 ethnically and racially diverse adults with extrapulmonary dissemination of coccidioidomycosis. Filtering the data for variants in genes involved in immune responses, we noted the presence of many polymorphisms in CHIT1. The product of this gene is a human chitotriosidase elaborated by phagocytic cells and previously shown to exhibit antifungal activity. To test the hypothesis that this chitinase modifies the course of *Coccidioides* infection, we examined serum chitinase activity in groups of individuals with varying severity of coccidioidomycosis.

Methods

Peripheral blood was obtained from a group of 85 ethnically and racially diverse adults with an age range of 19 to 92 years, including 55 Hispanic/Latinos, 24 Caucasians, 5 African-Americans, and 1 Filipino. The 72 individuals with proven coccidioidomycosis included 27 with mild pleural/pulmonary disease, 4 with prior severe pulmonary disease with respiratory failure, 27 with coccidioidal meningitis, and 14 with extrapulmonary disease without meningitis. Serum chitinase activity was quantified in a fluorometric assay by detection of hydrolysis of an artificial substrate, 4-methylumbelliferyl β–D-N,N',N''-Triacetylchitotriose (Sigma-Aldrich).

Results

Serum chitinase varied over a 60 fold range and differed among the 5 groups of enrollees, with no significant differences between the racial/ethnic groups ($p=0.13$ by ANOVA). A significant difference in serum chitinase was detected between groups ($p=0.03$; ANOVA). Moreover, mean serum chitinase values were significantly lower among individuals with coccidioidal meningitis than those with extrapulmonary disease without meningitis ($p<0.05$).

Conclusion

In this pilot study, lower serum chitinase levels were found among individuals with coccidiodal meningitis than among those with more limited extrapulmonary disease. Prospective studies are needed to examine the extent to which this product of phagocytic cells alters the extrapulmonary dissemination of *Coccidioides* infection.

COCCIDIOIDIN SKIN TEST IN TWO ENDEMIC AREAS OF COCCIDIOIDOMYCOSIS IN MÉXICO

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Introduction

In 2014, in the United States of America, the states of Arizona and California have reported an incidence of 5,624 and 2,243 coccidioidomycosis human cases respectively. In Mexico the last national epidemiological report, that refers the incidence of confirmed coccidioidomycosis cases was published in 1994, with an unexpected geographical distribution: the states with the highest incidence were Chiapas (in southeastern) and Tamaulipas (northeast), reporting 161 and 80 cases respectively. Previous studies have demonstrated the presence of *Coccidioides* in the soil and rodents with anti-*Coccidioides* antibodies in the city of Hermosillo, Sonora state, border with Arizona and in the town of Valle de Las Palmas located in Baja California state, border with California. The objective of this study was to investigate the prevalence of positive coccidioidomycosis skin tests in humans on two Mexican populations located in Sonora and Baja California.

Methods

Four applications of intradermal reaction with coccidioidina antigen, were carried out, two of them in the city of Hermosillo and the other two in the town of Valle de Las Palmas, in both populations the test was applied in the rainy season (November 2015) and in the dry season (May 2016).

Results

In Hermosillo, a total of 274 tests were applied and 152 (55.4%) were positive from which, 62 (46.6%) were in rainy season, and increased to 90 (63.9%) in dry season. For Valle de Las Palmas a total of 273 tests were applied, of which 18 (6.6%) were positive: 5 (3.6%) in November and the number was increased to 13 (9.6%) in May.

Conclusion

The prevalence of positive coccidioidomycosis tests was higher in the population of Hermosillo compared to Valle de Las Palmas and suggest a higher incidence of this mycosis in this region, evidencing underreporting of the disease. This study shows that climatic factors have an influence in the prevalence of positive tests in these regions.

SPECIMEN SOURCE AS A DETERMINANT OF UTILITY FOR REAL-TIME PCR IN THE DETECTION OF *COCCIDIOIDES IMMITIS* IN THE CLINICAL SETTING AT THE CENTRAL CALIFORNIA SAN JOAQUIN VALLEY

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Introduction Recently, a collaborative study between UCSF Fresno and the Microbiology department of CRMC validated the development of a real-time PCR assay for *Coccidiodes immitis* using a BD-Max machine. The experience proved that clinically relevant information can be available within 4 h using an RT-PCR method on the new machine. A follow-up clinical study showed that the sensitivity was 56.2% vs 45.2% for fungal culture while the specificity was 100%. The results mirrored earlier studies in Mayo Clinic by Binnicker and colleagues.
This study aims to examine the variability in utility of the test based on source of specimens.

Methods From March 1, 2014 through Dec 31, 2016, we were able to do a retrospective analysis of 1160 specimens of cerebrospinal fluid, bronchioalveolar lavage fluid, lung tissue biopsy, sputum and pleural fluid, for which Cocci PCR was ordered. We counted as positive disease those who were identified as proven or probable based on the ATS criteria for diagnosis of Coccidioidomycosis. Simple descriptive statistics were then used to analyze the data.

Results All of the 113 specimens that tested positive for Cocci PCR had positive disease, giving a 100% specificity for the test regardless of the specimen source. Sensitivities are shown:

Source	True Neg	False Neg	True Pos	Sens	95% C.I.	NPV
CSF	282	13	19	59%	42%-74%	98%
BAL	259	4	42	91%	80%-97%	96%
Lung Tissue Biopsy	258	20	16	44%	30%-60%	93%
Sputum	113	2	30	94%	80%-98%	98%
Pleural Fluid	95	1	6	86%	49%-97%	99%
Total	1007	40	113	74%	66%-80%	96%

There are statistically significant differences when comparing sensitivities for CSF vs BAL ($p<0.001$), CSF vs sputum ($p=0.00117$), for lung tissue vs BAL ($P<0.001$), lung tissue vs sputum ($p<0.001$), and lung tissue vs pleural fluid ($p=0.045$)

Conclusion We were able to show that the Cocci-PCR test using the BD-Max system is a viable and usable test for Coccidioidomycosis in the clinical setting here in Central California. When compared with the gold standard of fungal cultures, it had a better overall sensitivity (74% vs 45%) and was resulted in 4 hours rather than 1-2 weeks. While the specificities and PPVs were excellent for all the specimens at 100% each, sensitivities varied significantly based on the source of the specimen. CSF and lung tissue biopsies were worse at 59% and 44% respectively, while BAL (91%), sputum (94%) and pleural fluid (86%) were better.

ATYPICAL MANIFESTATIONS OF CENTRAL NERVOUS SYSTEM COCCIDIOIDOMYCOSIS

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Introduction

Central nervous system (CNS) involvement is reported in approximately 33-50% of patients with disseminated Coccidioidomycosis. The most common presentations are basilar meningitis and hydrocephalus, while mass lesions are much less frequently reported. Our objective is to describe three cases of atypical CNS Coccidioidomycosis.

Case Findings

We reviewed 3 cases of CNS Coccidioidomycosis complicated by mass lesions seen at a single institution. Average age was 64.7 years, and 2 were male. All were Caucasian and non-native Arizona residents. Case C had previously received prednisone for ulcerative colitis, while the other two were immunocompetent. Case A presented with diplopia following recent diagnosis of acute pulmonary Coccidioidomycosis; neurological exam showed left abducens nerve palsy. Brain MRI revealed abnormal bilateral orbital infiltrative soft tissue with dural enhancement. Cerebrospinal fluid analysis was consistent with Coccidioidal meningitis. Both cases B and C had a known history of Coccidioidal meningitis, diagnosed 6 and 2 years prior to presentation, respectively, and treated with fluconazole then switched to voriconazole due to lack of adequate treatment response initially. Case B presented with right facial droop and hearing loss. Brain MRI revealed a 14.5 x 22 mm contrast-enhancing, irregularly-shaped right cerebellopontine angle mass. Case C developed lower back pain and urinary incontinence. Lumbar spine MRI revealed a contrast-enhancing lesion within the spinal canal extending from L3 to L5.

Clinical Course

Case A was treated with intravenous amphotericin B in addition to fluconazole. Repeat MRI brain showed improvement in dural enhancement though he deteriorated clinically in spite of aggressive antifungal therapy. Surgical resection of respective masses was performed in cases B and C; pathology findings were consistent with Coccidioides.

Outcome

Case A died of multi-organ failure in the setting of his disseminated Coccidioidomycosis. Both cases B and C had clinical improvement following Coccidioidoma resection and adjustments to antifungal treatment.

Conclusion

These cases highlight the varied presentations of Coccidioidomycosis related mass lesions in the CNS, as well as the importance of remaining vigilant of these complications in patients already on azole therapy for *Coccidioides* meningitis.

MODELING AND MAPPING OF *COCCIDIODES* SOIL HABITAT

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Introduction

The saprophytic stage of *Coccidioides spp* exists in the soil and depends on certain soil properties with climatic conditions also exerting influence on its habitat. Current understanding of the geographic distribution of Coccidioides is primarily defined by data from skin test studies performed in the late 1940s and 1950s and also by outbreaks outside of these historically-defined areas. *Coccidioides* testing in soil has indicated patchy distribution. We developed a model to identify suitable habitats for Coccidioides in soils of the western United States based on attributes similar to locations where the fungus has been identified.

Methods

The United States Department of Agriculture, Natural Resources Conservation Services maintains a database with information about soils called the Soil Survey Geographic Database (SSURGO). SSURGO parameters in the model include organic matter content, pH, salinity, water holding capacity, electrical conductivity, temperature, and precipitation. A fuzzy system model was developed to determine a habitat suitability index for *Coccidioides*, ranging from 0 to 1. We mapped the index variables from the soil survey spatial data visually using a geographic information system. The scale of the resulting map is in the range of the soil survey, 1:24,000 to 1:12,000; thus, the resolution of the display is 540 times that of a 1:13,000,000 scale map (which depicts the western United States on a page). This allows possible habitat areas as small as a few hectares to be identified.

Results

The mapping shows that the distribution of suitable habitat on the landscape is not uniform. The model accurately identifies known historically endemic areas, such as Phoenix, Arizona and the San Joaquin Valley, California as being highly suitable for *Coccidioides*. Additionally, the model predicts outliers where the spatial and temporal conditions relative to temperature and rainfall may provide a suitable habitat in some years but not in others. Some of these outliers have been sites of coccidioidomycosis outbreak including Swelter Shelter, Dinosaur National Monument, Utah, and areas of northern California. In the Pacific Northwest, the model also predicted areas in South-central Washington State where locally-acquired cases were identified.

Conclusion

Increased understanding of habitat suitability for *Coccidioides* is important as a marker of geographic risk for public health and healthcare providers. Awareness of likely *Coccidioides* soil habitats could help the public and industry mitigate risk when conducting soil-disturbing activities and could help providers improve diagnosis and treatment of ill persons.

EX VIVO CYTOKINE RELEASE IN SUBJECTS WITH NEWLY DIAGNOSED *COCCIDIOIDOMYCOSIS.* ANALYSIS OF THIRTY CYTOKINES

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Introduction

Using current methods, the diagnosis of coccidioidomycosis may be delayed and prognosis cannot be precisely determined. Measurement of the coccidioidal-specific cellular immune response could result in both earlier diagnosis and give insight into outcome. *Ex vivo* release of cytokines (CK) after antigen stimulation of whole blood is a relatively simple method to measure the cellular immune response to infection. Because multiple cytokines (CK) can be measured, a complex picture of the cellular immune response may be elicited. We designed a study to assay multiple CK among patients referred for newly diagnosed coccidioidomycosis.

Methods

Patients seen for the first time for the diagnosis of coccidioidomycosis were eligible for enrollment. Those with a diagnosis of coccidioidal meningitis were excluded. After informed consent, 5 mL of blood was collected into sodium heparin and incubated with 20 μg/mL T27K, a coccidioidal antigen preparation, or nothing (control) for 18 hr at 37°C in 5% CO_2. The supernatant was collected and frozen at -80°C until assayed using the Luminex® magnetic bead multiplex system that assays 30 CK.

Results

To date, 34 subjects have entered the study. Their median age was 64 (27-80) years; 32 were male and 24 were white, non-hispanic. The median time from diagnosis to assay was 15 (6-386) days. Eighteen had an underlying disease, including diabetes in 11, lung disease in 8, cancer in 6, heart disease in 4, and rheumatological disease in 2. Two were on immunosuppression medications. In 27 instances, the patients had pulmonary coccidioidomycosis; 5 had positive serology only; and 2 had extrathoracic dissemination. Twenty-seven had a positive complement fixation titer at the time of assay. The median complement fixation titer for those positive was 1:4 (negative - 1:64). Seven were on antifungal therapy at the time of the assay (fluconazole 6; itraconazole 1). Eight had a coccidioidal skin test performed and it was positive in 5. The median diameter for those 4 who were positive with a diameter recorded was 12.5 (5-40) mm.

Among the 30 CK assayed, the mean antigen-stimulated concentration was ≥10-fold above control for only seven. These included 3 T-helper type 1 CK: IFN-γ, IL-2, and TNF-α and 4 inflammatory CK: GM-CSF, IL-1RA, IL-1β, and IL-13. CK among the 23 that were not elevated included IL-4, IL-10, IL-12, and IL-17. Of the cytokines analyzed, IL-2 was the most discriminatory, with a median concentration of 679 pg/mL above control (130-fold). There was no correlation to type of coccidioidomycosis. All 7 CK concentrations tended to be higher in those with positive CF titers.

Conclusion

There is a robust expression of CK after *ex vivo* antigen stimulation in recently diagnosed coccidioidomycosis. These could predate the expression of other tests for the diagnosis of coccidioidomycosis. In addition, the pattern of CK expression could yield information about the prognosis of coccidioidomycosis.

ANALYSIS OF SKIN TEST RESPONSES TO SPHERULIN-BASED COCCIDIOIDIN (SPHERUSOL) AMONG A GROUP OF SUBJECTS WITH VARIOUS FORMS OF ACTIVE COCCIDIOIDOMYCOSIS

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Introduction

The role of recently released Spherusol® spherule-based coccidioidin skin test in the management of patients with coccidioidomycosis is currently undefined. Older studies with a previous formulation have suggested that a positive delayed-type hypersensitivity reaction to coccidioidin is associated with an improved outcome and a lower risk of recurrence when antifungal therapy is discontinued. To begin to assess this with the new formulation, we correlated the results of skin test reactivity to Spherusol® with other clinical factors associated with coccidioidomycosis.

Methods

Patients followed in the coccidioidomycosis clinic at the Southern Arizona Veterans Affairs Health Care System (SAVAHCS) were eligible. Those with a diagnosis of coccidioidal meningitis were excluded. After informed consent, 0.1 mL of Spherusol® was injected intradermally into the volar aspect of the left forearm. Induration was measured 48 hours later and recorded. The study was supported by a grant from Nielsen BioSciences.

Results

Twenty-seven subjects have participated to date. Twenty-four were male and 19 were white, non-hispanic. The median age was 63 (28-80) years. Sixteen had an underlying disease including diabetes (8), lung disease (5), cancer (5), rheumatologic (4), transplantation (1) and 7 were on immunosuppressive medications. There was a median of 15.4 months (8 d to 31 years) from diagnosis to the placement of the skin test. Fifteen had pulmonary coccidioidomycosis, 8 were disseminated and 4 were positive coccidioidal serology only. Thirteen were on oral triazole antifungal therapy.

The skin test was positive in 15, including 9 with pulmonary, 4 with disseminated, and 2 with serology only (P=0.874). The median diameter of induration in those who were positive was 20 (13 - 30) mm. Five of 8 with negative complement fixation antibody (CF) and 10 of 19 with a positive CF had positive skin tests (P=0.637). In those with a positive skin test, there was no association between the skin test diameter and the CF titer (P=475). Ten of 14 not on antifungal therapy had a positive skin test compared to 5 of 8 not on therapy (P=0.085) and 13 of 20 not on immunosuppressives were positive compared to 2 of 7 on such therapy (P=0.095).

Conclusion

More than half of the subjects had a positive Spherusol® skin test. There was no significant relation with other factors associated with outcome in coccidioidomycosis, but there was a trend toward reactivity in those not on antifungal therapy and not on immunosuppressives. At this time, no overall assessment about outcome and skin test reactivity can be made. However, with further follow-up, this is likely possible.

INVESTIGATING DIFFERENTIAL EXPRESSION UTILIZED DURING THE FUNGAL MORPHOGENESIS OF THE ATTENUATED STRAIN OF COCCIDIOIDES POSADASII

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Introduction

The soil dwelling fungi, Coccidioides immitis and C. posadasii have a complex life cycle that changes dramatically from saprobic to parasitic upon exposure to a mammalian lung. What causes the morphological switch is not well characterized but it is generally agreed that the change in life cycle initiates host infection, causing the disease coccidioidomycosis also known as valley fever. A previous study investigated the differential expression of the vegetative and parasitic life cycle of Coccidioides strain C735 and identified an up regulation of 1,880 genes in the parasitic lifecycle. However, characterizing the function and role of 1,880 genes is untenable. To reduce the number of genes of interest, this study compared the transcriptome of the parasitic life cycle between Coccidioides strain C735 and an existing attenuated derivative. Attenuation was achieved through the deletion of the cts2/ard1/cts3 genes, resulting in a mutant strain that can form sterile spherules but not endospores.

Methods

Spherule cultures were grown in modified Converse media at 39C and 10% CO_2 for 48 hours. Total RNA was extracted using Trisure, mRNA was isolated using NEBNext beads and sequencing was performed on an Illumina MiSeq platform. Analysis of differential expression was completed using the Tuxedo suite.

Results

The parasitic life cycle of C735 and the attenuated derivative shared genes with both increased and decreased expression when compared to the vegetative lifecycle. Several down regulated genes were related to cell wall organization where many up regulated genes were associated with oxidation-reduction processes. Comparison of the parasitic life cycle between the two strains indicated thirty-six genes that were up regulated 2 fold or higher in C735 but were not expressed in the attenuated derivative. The majority of these genes are categorized as hypothetical or predicted proteins.

Conclusion

The morphological shift, which instigates host infection, is uncharacterized. Understanding these mechanisms is an important part of the infection dynamic. The attenuated derivative of C735 is able to develop into spherules but not rupture, releasing infectious endospores. This comparison elucidates the genetic pathways that are affected by attenuation and are therefore crucial to pathogenesis and establishment of infection. The thirty-six genes that are expressed during the parasitic lifecycle of C735 and not the attenuated derivative are logical targets for gene function studies.

CHARACTERIZATION AND MANAGEMENT OF COCCIDIOIDOMYCOSIS IN PATIENTS TREATED WITH INHIBITORS OF TUMOR NECROSIS FACTOR-*ALPHA*

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Introduction

Tumor necrosis factor inhibitors (TNFIs) are common therapies for many autoimmune and inflammatory conditions. Because TNFIs decrease the efficacy of the cellular immune system, their impact of coccidioidomycosis requires further study. While prior smaller studies are helpful, we lack large-scale descriptions of clinical manifestations of coccidioidomycosis and its optimal treatment in TNFI recipients, leaving lingering questions on how to best approach such infections. Our aim was to describe clinical manifestations and treatment approaches for both antifungal and TNFI medications in TNFI recipients at our institution whose course was complicated by coccidioidomycosis.

Methods

Prior to starting TNFI, patients are screened for coccidioidomycosis. Testing may be repeated prn suggestive symptoms. We conducted an electronic medical record search to identify all patients who received selected TNFIs (infliximab, etanercept, adalimumab, certolizumab or golimumab) at our institution between 4/4/2010 to 9/26/2016, with coccidioidomycosis seropositivity. We then performed retrospective review of patient records, and collected clinical, laboratory, radiographic data on patients with proven or probable coccidioidomycosis.

Results

1189 patients were prescribed TNFI and had any testing for coccidioidomycosis, of which 28 patients (2.4%) had proven or probable coccidioidomycosis. Of these 28, 17 (61%) were male, and all were Caucasian; adalimumab (n=14, 50%), infliximab (n=7, 25%), and etanercept (n=5, 18%) comprised the majority of TNFIs. Underlying inflammatory diseases included gastrointestinal (n=13, 46%), rheumatologic (n=13, 46%) and dermatologic (n=2, 7%) conditions. 7/28 (25%) had proven and 21/28 (75%) probable infection, and 5/28 (18%) had extrapulmonary dissemination. 24/28 (86%) patients in total had TNFI held due to coccidioidomycosis; of these, 8/24 (33%) ultimately restarted a TNFI and 0/8 experienced a relapse in clinical infection. Of those treated with an antifungal, 12/28 (43%) were treated for ≤ 12mo while 16/28 (57%) were treated for lifelong or indefinite antifungal therapy. Among the 4 patients continued on TNFI, none had evidence of reactivation, dissemination or death.

Conclusion

Coccidioidomycosis in TNFI recipients is not common, but has high rate of dissemination. Despite this, not all required discontinuation of TNFI for control of infection and those that continued TNFI without interruption were not complicated by progression of infection. Treatment with azoles universally controlled coccidioides infection.

EXPLORING THE DISTRIBUTION OF *COCCIDIOIDES IMMITIS* IN SOUTH CENTRAL WASHINGTON STATE

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Introduction

Coccidioides spp have historically been found in the southwestern United States and parts of Mexico and Central and South America. However, in 2010 there were three coccidioidomycosis cases in Central Washington. Colonization of soils by *C. immitis* have been confirmed at exposure sites associated with these cases. Multiple studies have identified a relationship between environmental conditions and *C. immitis* growth areas, but these relationships have not been evaluated in Washington. The Washington State Department of Health has been conducting environmental surveillance in an effort to understand the geographic distribution of *C. immitis* in central Washington and the associated risk to humans and animals. Here we describe our environmental surveillance efforts and present preliminary findings related to environmental conditions of *C. immitis* growth areas in central Washington.

Methods

We collected soil samples at potential human exposure sites in central Washington, identified through clinical surveillance and patient interviews. Soil samples were analyzed by the U.S. Centers for Disease Control and Prevention using real-time PCR that detects *Coccidioides*-specific targets. We employed data from the USDA Soil Survey Geographic (SSURGO) database to describe conditions associated with positive samples. We used our findings to identify un-sampled regions of central Washington that could potentially support *C. immitis* growth.

Results

We detected *Coccidioides* in soil from multiple sampling sites. Some positive samples were from regions outside of previously described growth areas in central Washington. We identified a band stretching across central Yakima and Benton counties with soil characteristics similar to those of positive sample sites.

Conclusion

Coccidioidomycosis is emerging in south central Washington, and the ecology and geographic distribution of the pathogen are poorly understood. The similar soil characteristics across central Yakima and Benton counties suggests these regions could potentially support the growth of *C. immitis*. We found that *C. immitis* presents a risk to humans and animals across a larger region of central Washington than previously described, highlighting a need for continued environmental surveillance. The potential growth sites we identified also provide a valuable tool for human and veterinary health care providers and public health practitioners to understand geographical risk for disease. This can increase efforts at testing and diagnosing patients from this region.

DIGGING UP DISEASE: ENVIRONMENTAL SURVEILLANCE FOR *COCCIDIOIDES IMMITIS* IN WASHINGTON

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Introduction

Since 2010, there have been 11 reported human cases of Washington State-acquired coccidioidomycosis. However, only a few soil samples from localized areas within two counties have tested positive for *Coccidioides immitis* DNA. The discrepancy between epidemiological and environmental data indicates that more field surveillance of *C. immitis* in Washington may be important to identify hotspots and regional distribution in the environment. The occupational risk involved in environmental surveillance for *C. immitis* is the disturbance of soil and potential inhalation of the 2-5 μm arthrospores. This requires that extensive personal protective equipment (PPE) be worn and decontamination protocols followed during all field sampling events. Also, since *C. immitis* is a biological safety level 3 pathogen, it must be handled with a high level of biosecurity when soil is analyzed for detection of *C. immitis* DNA. We developed a protocol for appropriate PPE when field sampling for *Coccidioides*.

Methods

In our protocol, we prescribe respiratory protection provided by a half-face mask or Powered Air Purifying Respirator (PAPR) equipped with P-100 filters for field activities. We prescribe full coveralls and nitrile gloves to limit the risk of transporting *C. immitis* arthrospores on clothing or skin. We suggest Tyvek suits and boot covers, but these should be used with discretion in public settings since they can cause public concern. For biosecurity during soil analysis, we have implemented a hybrid DNA extraction technique that is started in the field and finished in the laboratory after the pathogen is neutralized.

Results

Adequate field PPE and the hybrid field/lab DNA extraction method mitigates danger to the sample processor in the field and lab while allowing for rapid processing of soil and detection of *C. immitis* DNA.

Conclusion

Employing appropriate respiratory protection against exposure to virulent arthrospores is likely to address the major concern of occupational safety during field surveillance. The hybrid field/lab DNA extraction improves processing efficiency and reduces the potential for contamination of samples during the extraction process compared to performing the complete DNA extraction in the field. Field surveillance for *C. immitis* in Washington should help inform physicians and veterinarians of associated environmental risks to patients

ADVANCES IN SOIL SAMPLING METHODOLOGY IN WASHINGTON STATE

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Introduction

Washington's *Coccidioides* research uses a One Health surveillance approach combining human, veterinary, and environmental surveillance to help understand the potential geographic distribution in the environment. While the human and veterinary aspects of research conducted on *Coccidioides* are well documented, environmental surveillance methodology is lacking. Previous attempts at random environmental sampling for *Coccidioides* have been ineffective. Therefore, we have developed a methodology for soil sampling targeted in locations where an exposure is suspected to have occurred. A secondary objective of the soil sampling is to describe the ecological niche for *Coccidioides* in parts of southcentral Washington. Here, we present results of a pilot systematic method of soil sampling to screen areas where suspect human exposures may have occurred.

Methods

Through patient interviews with coccidioidomycosis cases, questions about dust exposure and symptom onset were used to identify locations of suspected exposure to *Coccidioides*. We accomplished environmental testing by laying out transect lines over a landscape with adjoining 10 meter diameter plots 50 – 100 meters apart. We practiced soil sample compositing and took three stratified composite samples randomly from each plot at zero to three inches and three to six inch depths, and from rodent holes if present. In addition to real-time PCR analysis for *Coccidioides*, several soil parameters are determined at the time of sampling that help inform that model: pH, electrical conductivity, soil moisture, soil temperature, and quantifiable soil texture. We applied this screening method to a privately owned farm in southcentral Washington State where a case-patient works and lives, and reported soil-disturbing activities.

Results

At this suspected exposure location, we detected *Coccidioides* in the soil in 3 of 33 established plots sampled.

Conclusion

In this proof of concept for our systematic soil sampling, we were successful in identifying *Coccidioides* DNA at the suspected exposure site of a case-patient. This systematic approach for conducting soil surveillance activities presents a methodology that promises to economize resources and correlate data with rodent activity. Defined soil parameters can help define the ecological niche of this fungus in Washington.

COCCIDIOIDOMYCOSIS MENINGITIS WITH HYDROCEPHALUS AND SHUNT REVISIONS

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Introduction

Coccidioidomycosis results from the dimorphic fungi of the genus *Coccidioides* (*C.immitis* and *C.posadasii*). Coccidioides immitis is endemic to the southwestern United States. It can present as sub-clinical, pulmonary, or disseminated infection. The most lethal complication of the infection is meningitis. If left untreated this can result in death for 95 percent of patients within two years. Coccidioidal meningitis can present with non-specific symptoms, but headache is present in almost 75 percent of patients. Lumbar puncture is necessary in diagnosis. A complication of this disease is increased intracranial pressure which can result in the development of hydrocephalus. A shunt is usually necessary in patients who develop hydrocephalus. Shunts can have complications, that may include but are not limited to: obstruction, infection, and/or failure.

Methods

Data Collection –In this retrospective study, 56 patients were identified with inclusion criteria of having coccidioidal meningitis with hydrocephalus requiring a shunt. Data was collected through uniform query of community hospital database from the years 2007-2017. Data was collected on patient demographics, medical history, social history, number of revisions and the time between each revision.

Results

Of the 56 patients, 20 had zero revisions, 12 had had 1 revision, 18 had 2-4 revisions, and the remainder had multiple revisions. Of the patients who had ventriculo-peritoneal (VP) shunt placement, 30 were Hispanic, 12 Caucasian, 8 African American, and 6 other ethnicities. Of the subset that needed at least one VP shunt revision, 20 were Hispanic, 8 Caucasian, 7 African American, and 1 other ethnicity. Of the 56 patients who required VP shunt placement 36 were males. Of the subset who required at least one revision, 21 were males. The average age of patients requiring at least one shunt revision was 44. BMI of requiring at least one shunt revision was 27.6. Of the 36 patients who required at least 1 revision, only 4 had diabetes mellitus, and if hemoglobin A1C was 9 or greater, they required at least 2 revisions. Of the patients requiring at least 1 revision, 14 had hypertension, 7 had dyslipidemia, 1 had HIV, none had pulmonary tuberculosis and 9 had tobacco dependence. Of the patients who had at least 1 revision, 16 had a revision within first 12 months while 5 had a revision within 24 months. Of the patients who had a shunt complication within the first 12 months, they were more likely to have additional revisions.

Conclusion

More than one half of patients with coccidioidial meningitis with hydrocephalus who had shunt placement required at least one revision. The placement of a shunt can lead to infection or failure of he shunt requiring a revision in 72% or our patients. If the patient is a Hispanic male, there is increased likelihood of a V-P shunt revision based on our data collection. Further studies are warranted to determine the impact of shunt placement and other variables associated with complications.

SURGICAL MANAGEMENT OF SPINAL COCCIDIOIDOMYCOSIS: SANTA CLARA VALLEY MEDICAL CENTER EXPERIENCE

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Introduction

C. immitis fungus is endemic to the American South West. Usual clinical manifestations are pulmonary. One percent of patients develop extra pulmonary dissemination, usually to the central nervous system or surrounding structures. Spinal manifestations include osteomyelitis, epidural compression, and intradural extension. Neurosugical management is often indicated for mechanical instability, neurologic deficit, intractable pain, or disease progression despite antifungal therapy.

Methods

Retrospective chart reviews were made of inpatient consults to the neurosurgical service for evaluation of osteomyelitis from *C. Immitis* from 2012-2017.

Case Findings

Cases fell into two broad surgical categories involving all parts of the spine:

1. Mechanical instability/ pain
2. Neurologic deficits

Case illustrations were provided for osteomyelitis, epidural and intradural extension, with surgical outcomes.

Results

We identified six patients with vertebral involvement from *C. immitis*. Four patients required surgery. Surgical cases included vertebral osteomyelitis, epidural phlegmon, and intradural abscess/phlegmon. All patients had neurological deficits as it related to level of spine involvement. Operative debridement and stabilization were performed.
Improvement was in both pain and neurologic function in three patients with vertebral and epidural involvement. The one patient identified with intradural extension had no neurologic improvement with findings of severe arachnoiditis at the time of surgery.

Conclusion

Vertebral infection caused by coccidioidomycosis requires a multidisciplinary approach that includes aggressive medical therapy and often surgical intervention for debridement, stabilization and decompression of the neural elements. While surgical intervention is rare, it can provide improved outcomes in selected cases. Discontinuation of medical therapy is often associated with a high risk of relapse.

COMPARISON OF IMMUNODIFFUSION (ID), COMPLEMENT FIXATION (CF) AND MVista ENZYME IMMUNOASSAY (EIA) FOR DETECTION OF ANTI-*COCCIDIOIDES* ANTIBODIES

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Background

Recently, a semi-quantitative EIA for measurement of IgG and IgM anti-*Coccidioides* antibodies was developed that is more sensitive than ID or CF [1]. We sought to evaluate the performance of this assay in specimens that were positive using a commercial anti-*Coccidioides* antibody (EIA).

Methods

Between February 2016 and May 2017, 91 patient sera that were positive in the commercial EIA kit (Premier *Coccidioides* EIA, Meridian Bioscience) performed during routine testing at UCLA Health System were tested blindly in the MVista EIA, performed at MiraVista Diagnostics. ID tests were performed at UCLA clinical pathology laboratory using commercial reagents obtained from Meridian Bioscience, Inc., and CF tests were performed at Quest Diagnostics.

Results

The sensitivities of the antibody tests are shown in the table. The MVista EIA detected antibodies in 91% of specimens that were positive by ID. ID detected antibodies in 61% of patient sera that were positive by MVista EIA. The MVista EIA detected antibody in 96% of specimens that were positive by CF at a titer of ≥1:2 and 80% that detected antibody at a titer of undiluted or higher. The CF was positive at a titer of ≥ 1:2 in 39% of specimens that were positive in the MVista EIA and at a titer of undiluted or higher in 87%.

Test	Positive	Total	%
MVista IgM	56	87	64
MVista IgG	58	84	69
MVista IgM or IgG	70	89	79
IDTP	34	81	42
IDCF	26	88	30
ID TP or ID CF	48	91	53
CF ≥ undiluted	71	85	84
CF ≥1:2	26	85	31

Conclusion

These findings suggest that the EIA is more sensitive than ID and CF using certain commercially available reagents or reference laboratory services.

(1) Malo J, Holbrook E, Zangeneh T, et al. Enhanced Antibody Detection and Diagnosis of Coccidioidomycosis with the MiraVista IgG and IgM Detection Enzyme Immunoassay. J Clin Microbiol 2017 Mar; 55(3):893-901.

EVALUATION OF THE MVista ANTI-*COCCIDIOIDES* ANTIBODY ENZYME IMMUNOASSAY (EIA) FOR DETECTION OF ANTIBODIES IN CEREBROSPINAL FLUID (CSF)

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Background

Detection of antigen by EIA and antibody by CF in the CSF are useful methods for diagnosis of *Coccidioides* meningitis. The sensitivity for detection of antigen was 93% compared to 70% for CF [1]. We have developed an anti-*Coccidioides* antibody EIA that is more sensitive than CF or detection of antibody in serum, 88% and 64%, respectively [2]. Another potential benefit of the EIA is high inter-assay reproducibility of semi-quantitative results. The purpose of this study was to compare the EIA with CF for detection of antibodies in the CSF.

Methods

Consecutive de-identified CSF specimens from patients at Banner Health Medical Centers in the Phoenix, AZ area had been submitted to their reference laboratory, Sonora Quest Laboratories in Tempe, AZ, for CF testing for diagnosis of suspected meningitis were stored frozen and submitted as a single batch to MiraVista Diagnostics. No clinical information was collected.

The CSF specimens were diluted 1:25 in StartingBlock rather than 1:1000 as used for serum [2]. Unit values corresponding to antibody levels were calculated by extrapolation from a standard curve containing five standards spanning the range from 0 to 80 units. Results were reported semi quantitatively in antibody units. The cut off for antibody detection was 10 units. CF testing was performed at Quest Diagnostics.

Results

The agreement between CF and EIA are shown in the table 1. All CF positive specimens were positive by EIA. Three CF negative specimens were positive by EIA for IgG antibodies and one for IgM antibodies. Semi-quantitative IgG levels did not correlate with CF titers. Specimens were tested on two occasions by the EIA and results showed excellent agreement.

Table 1.	**AB IgG+**	**AB IgG-**	**AB IgM+**	**AB IgM-**	**AG+**	**AG-**
CF+ (n=8)	100%	0%	100%	0%	83%	17%
CF- (n=41)	7%	93%	2%	98%	0%	100%

Conclusion

The EIA appears to be a sensitive method for diagnosis of Coccidioides meningitis, a hypothesis that requires assessment in a larger clinical trial. These findings support evaluation of the EIA and a larger clinical study.

(1) Kassis C, Zaidi S, Kuberski T, et al. Role of Coccidioides Antigen Testing in the Cerebrospinal Fluid for the Diagnosis of Coccidioidal Meningitis. Clin Infect Dis 2015 Nov 15; 61(10):1521-6.

(2) Malo J, Holbrook E, Zangeneh T, et al. Enhanced Antibody Detection and Diagnosis of Coccidioidomycosis with the MiraVista IgG and IgM Detection Enzyme Immunoassay. J Clin Microbiol 2017 Mar; 55(3):893-901.

THE EFFECTS OF CLIMATE ON VALLEY FEVER INCIDENCE IN THE SOUTHWESTERN UNITED STATES

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Introduction

Previous studies examining the relationship between valley fever incidence and climate focused on a few, highly endemic counties. Furthermore, studies have been limited by the lack of a regional valley fever incidence database. Our study builds upon these analyses by compiling a regional valley fever incidence database and exploring the spatiotemporal relationships between valley fever incidence and climate and environmental factors across the southwestern U.S.

Methods

We combined county-level valley fever cases provided by state health agencies to create a regional valley fever database, including Arizona, California, Nevada, New Mexico, and Utah. We estimated county-level valley fever incidence by dividing the number of monthly reported cases by annual county-level population. We compiled climate and environmental datasets from multiple sources to compare with valley fever incidence, including air temperature, precipitation, soil moisture, surface dust concentration, normalized difference vegetation index, and cropland area. Our analysis spanned 2000 to 2015, when month-level valley fever data was available for each county.

Results

Valley fever incidence was elevated in areas with warm air temperature and dry soils. The mean annual cycle of incidence varied across the southwestern U.S., and peaked following decreased environmental moisture. In the San Joaquin Valley of California, fall incidence followed cooler, wetter, and productive springs. Incidence in south-central Arizona significantly increased through time; by 2015, south-central Arizona had double the incidence rate compared to the San Joaquin Valley.

Conclusion

Our analysis provides a framework for interpreting the influence of climate change on valley fever incidence dynamics. Our results may provide information for the U.S. Centers for Disease Control and Prevention to improve their estimates of the spatial pattern and intensity of valley fever endemicity.

We are working to publish the valley fever incidence database as a resource to the valley fever community, upon permission of the state health agencies. Additional work includes compiling a soil sampling database denoting positive and negative soil samples for *Coccidioides* spp. This will be a publicly available database and useful for future niche modeling of *Coccidioides* spp. These databases will be available at https://github.com/mgorris/.

EXPLORING THE STRUCTURAL VARIATION AND EVOLUTION OF THE MITOCHONDRIAL GENOMES OF *COCCIDIOIDES IMMITIS* AND *C. POSADASII*

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Introduction

Coccidioides posadasii and *C. immitis* are soil-dwelling fungal species complexes that are responsible for thousands of human infections throughout the arid and semi-arid areas of the American continent. Based on whole genome sequencing, *C. immitis* harbors at least three populations: San Joaquin Valley, San Diego/Mexico and Washington. *C. posadasii* is distributed along Arizona, Texas/Mexico/South America and Caribbean populations and has a wide geographic distribution. Despite the great efforts to understand the population genetics of these microorganisms based on complete genomes, little was done about the structure and evolution of the mitochondrial genomes of those pathogen complexes.

Methods

The genomes of 186 *Coccidioides* spp. isolates were massively sequenced and assembled using Unmanned Genome Assembly Pipeline (UGAP). We used the complete *C. immitis* RS mitogenome as query sequence and by using Blastn we were able to retrieve those single or multiple contigs from each individual *Coccidioides* mitochondrial genome. The mitochondrial genes, introns and additional ORF's were predicted using the MFannot pipeline for 6 strains that represents the main *Coccidioides* lineages. Moreover, we compared the phylogenomic distribution of both nuclear and mitochondrial datasets.

Results

The mitochondrial genome size of *C. immitis* varied between 68kb and 73Kb while *C. posadasii* from 67kb to 82Kb. The gene content is similar to other Onygenanales as follows; ATP synthase (*atp6*, *atp8* and *atp9*), cytochrome b (*cob*), cytochrome c oxidase (*cox1*, *cox2* and *cox3*), NADH dehydrogenase (*nad1*, *nad2*, *nad3*, *nad4*, *nad4L*, *nad5* and *nad6*) and RNAse P (*rnpB*). In the other hand, the intron composition between *Coccidioides* spp. and other Onygenales changed dramatically, especially intron-types I and II. Genomic rearrangements within isolates from *C. posadasii* TUCSON population were observed. The phylogenomic trees from both nuclear and mitochondrial genes were congruent for most part of isolates and the population structure above cited was maintained. Interestingly, introgression with *Coccidioides* ssp. was also observed, since unique mutations observed in *C. posadasii* were also observed in few *C. immitis* strains.

Conclusion

We showed that polymorphisms observed in mitochondrial genomes are also useful for *Coccidioides* species discrimination at population level, but also fluctuates between species and populations as observed in other eukaryotes. The accumulation and distribution of introns-types I and II, especially within the genes *nad5*, *cob* and *cox1* in the *Coccidioides* genus and other Onygenales brings new opportunities to deeply investigate the evolutionary trajectory of those elements in the Ascomycota phylum.

A GLIMPSE INTO GENETIC VARIATION OF *C. POSADASII* IN THE ENVIRONMENT

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Introduction

Coccidioidomycosis is a deep animal systemic mycosis caused by the fungal species complexes *Coccidioides posadasii* and *C. immitis*. The fungus is found in the soil and upon inhalation by mammal hosts may colonize different tissues. The infection is often asymptomatic. *C. posadasii* has a wide distribution in the American continent ranging from Northern USA to Argentina. Extensive population genetics studies provided evidence for strong genetic differentiation of *C. posadasii* into three main populations: Arizona, Texas/Mexico/South America and the Caribbean. Within *C. posadasii* Arizona, clinical isolates cluster within Phoenix and Tucson sub-populations, however a third soil-derived population was found and has its own genetic trait suggesting that additional environmental genotypes may exist within *C. posadasii* species complex.

Methods

We used whole genome sequencing of environmental isolates and Illumina ITS-2 high throughput amplicon sequencing data from USA and Venezuela to compare the genotypes of *C. posadasii* from those recovered from human-derived samples. We used whole genome and ITS2 Single Nucleotide Polymorphisms discovery (SNPs) data in order to infer the phylogenetic distribution of clinical and environmental *C. posadasii*.

Results

Phylogenomic comparisons between *C. posadasii* clinical and soil isolates from Tucson indicates that the majority of soil-derived isolates clustered apart from patient samples. We also found few soil-derived isolates that share the same genetic trait of clinical derived samples suggesting pathogenic genotypes are also present in the soil. ITS-2 massive sequencing of soil samples from Venezuela and Tucson also revealed the presence of SNP's unique to soil-derived isolates suggesting additional genotypes of *C. posadasii* exist in the environment.

Conclusion

Taking these data together, we suggested that novel *C. posadasii* genotypes might be present in the environment. The variation observed in ITS-2 sequence within *C. posadasii* may be also an artifact generated by sequencing multiple copies of this fragment from a complex environmental source, which may generate spurious SNPs.

MOLECULAR DETECTION OF *COCCIDIOIDES POSADASII* IN ENDEMIC AREAS OF COCCIDIOIDOMYCOSIS IN VENEZUELA

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Introduction

Coccidioides immitis and *C. posadasii* are endemic fungal pathogens distributed throughout arid and semi-arid regions of the American continents. Genetic analysis suggests that the majority of clinical isolates recovered from South America belong to *C. posadasii* species. Little is know about the prevalence of species distribution and ecological factors that favor the occurrence of this pathogen in Venezuela.

Methods

We utilized qPCR-based approaches and deep ITS2 Illumina sequencing to detect *Coccidioides* spp. DNA was extracted from soil collected in endemic areas of the disease in Venezuela.

Results

A 3,806-fold variation of *Coccidioides* DNA was observed depending on the sampled location. Highly positive areas were found in Urumaco, Sucre and Democracia municipalities located in the coastal plains of the Paraguaná peninsula and the depression valleys of Lara and Falcon states. These areas are characterized by warm and dry climates, low altitude, xerophytic vegetation, sandy soils with high salt concentrations and alkaline pH, which may favor *Coccidioides* spp. growth and development. The whole mycobiome analysis of positive soils revealed the presence of two different *C. posadasii* OTU's: one phylogenetically related to clinical samples and a second genotype that clusters apart from *C. posadasii* strains to reveal that this species may contain soil-derived cryptic groups. Finally, we observed a decrease in diversity indexes when *C. posadasii* is abundant. This observation supports previous findings that *Coccidioides* inhabits specific environments which in turn selects for less diverse communities of fungal species.

Conclusion

These results indicate that *C. posadasii* is endemic to Venezuela, and varied amounts of *Coccidioides* DNA in the soil may result in different amounts of fungal inoculum. Consequently, different amounts of fungal soil inoculum would predict differential exposure to humans.

A RETROSPECTIVE REVIEW OF *DE NOVO* COCCIDIOIDOMYCOSIS AMONG REMOTE SOLID ORGAN TRANSPLANT RECIPIENTS AT MAYO CLINIC ARIZONA

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Background
Solid organ transplant recipients who reside in a *Coccidioides*-endemic region that acquire coccidioidomycosis are at risk for a complicated, protracted, disseminated and severe disease course compared to the general population. Following solid organ transplantation, anticoccidioidal prophylaxis for 6 to 12 months is recommended in patients without a history of coccidioidomycosis living in an endemic area. To date, there are no studies that describe coccidioidal infection, treatment, and outcomes in the transplanted patient on low dose, baseline immunosuppression that develops this illness after post-transplant year 1, and after discontinuation of azole prophylaxis. We aimed to describe the presentation, treatment, and outcome of coccidioidomycosis that developed in solid organ recipients at least one year after transplantation and following discontinuation of fluconazole prophylaxis.

Methods
This study was a joint project of Mayo Clinic AZ (MCA) and University of Arizona transplant teams. We conducted an electronic search of all patients with a history of solid organ transplantation from 11/1/1998 through 12/31/2015, and combined that list with a list of all patients who tested positive for coccidioidomycosis in the same time frame. This abstract summarizes the work done at MCA. We retrospectively reviewed the patients with no prior coccidioidomycosis, who developed coccidioidomycosis 1 year post-transplantation and after discontinuation of antifungal prophylaxis.

Results
We identified 35/4000 patients with solid organ transplants and *de novo* coccidioidomycosis that developed after 1 year following transplantation. Coccidioidomycosis presentations included asymptomatic seropositive patients (n=16/23, 69.6%), pulmonary coccidioidomycosis (n=16/34, 47%), and disseminated disease (n=1/35, 2.9%). Eighty-three percent of patients with pulmonary coccidioidomycosis were symptomatic. The single patient with disseminated disease was symptomatic, with infection. Seven of twelve (58%) of symptomatic patients were hospitalized. Thirteen of twenty-one (62%) of patients who were asymptomatic were not treated with any antifungal medication without sequeula, and 92% of symptomatic patients were treated with a triazole. No patient died from coccidioidomycosis.

Conclusion
Whereas coccidioidomycosis in newly transplanted patients on high level immunosuppression can be manifested by severe or disseminated disease, most of the transplant recipients with newly-developed coccidioidomycosis that manifested after post-transplant year 1 were asymptomatic, often requiring no antifungal therapy. This lower acuity coccidioidal infection coincides with lower levels of immunosuppression. However, severe or disseminated infections still occurred in patients, mandating the need for continued vigilance and caution.

SINGLE-SUBJECT TRANSCRIPTOME PROFILING OF STAT4 MUTANT PATIENT PBMCS SUGGESTS ALTERED RESPONSIVENESS TO COCCI LYSATE STIMULATION

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Introduction

The host response to coccidioimycosis exposure determines the clinical pathology. Understanding these responses is central to immune interventions for coccidioidomycosis.

Methods

In this pilot study, we used a novel k-means enrichment (kMEn) bioinformatics technique designed for whole transcriptome analysis in single subjects to determine personalized responses of patients with coccidioidomycosis diagnoses to *ex vivo* spherule lysate stimulation. We collected, stimulated, and RNA-sequenced PBMCs from a rare STAT4 mutated patient who presented in Arizona with disseminated coccidioidomycosis (MEND n=1), a patient with self-limiting pulmonary disease (PUL n=1), and a patient with disseminated coccidioidomycosis but no suspected monogenic susceptibility factors (DCM n=1).

Results

All patient PBMCs exhibited upregulation of genes for innate immune responses, inflammation, and chemotaxis. The patient with the STAT4 mutation was the least reactive in this assay, and further showed discordant responses in certain key immune pathways (ex. GO:0034341 Response to interferon-gamma) when compared to the other two patients. Analysis of transcription factor signatures using MSigDB and other literature-mined ChIP-Seq resources further suggested that there were fewer genes annotated as having STAT4 transcription factor binding sites that responded to stimulation in this STAT4 mutant patient. In addition, the transcription factor signature for STAT4 was less highly enriched in the stimulation-responsive genes of the mutated patient, though not absent (FDR 4.39×10^{-4} with 13 TRANSFAC overlapping genes in MEND vs enrichment FDR 9.43×10^{-8} with 28 matches and 6.43×10^{-9} with 32 matches in DCM and PUL, respectively). Complete analysis of these transcript patterns requires additional investigation and validation before strong conclusions can be drawn. This work is ongoing, and we are currently recruiting additional patients into our study.

Conclusion

These pilot data suggest that *ex vivo* spherule lysate exposure can provoke interpretable transcriptional responses, and that the STAT4 mutation observed in a rare patient with disseminated coccidioidomycosis has a functional response-dampening impact on activation of cocci-relevant genes and pathways.

IMMUNE BIOMARKERS OF *COCCIDIOIDES* DISEASE OUTCOME IN PEDIATRIC PATIENTS

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Introduction

Protective immunity against the fungal pathogen *Coccidioides* requires specific T helper cellular responses. Mouse vaccine and infection studies have defined T helper (Th)1 and Th17 cells in the resolution of infection and in effective protection. Patients with chronic *Coccidioides* infection and with disseminated disease demonstrate reduced cellular responses. Patients with abnormal IL-12/IFNγ signaling are more susceptible to disseminated disease. To define biomarkers of effective immune responses, peripheral blood immune populations were evaluated during acute infection and related by patient disease outcome.

Methods

PBMCs and serum where collected from 30 pediatric *Coccidioides* infected patients and 20 healthy controls in the San Joaquin Valley. Samples were evaluated by flow cytometry for percentages and total cellularity of innate and adaptive immune populations, and levels of inflammatory and helper cytokines. Clinical and flow data were evaluated according to disease outcome (resolved or chronic) using principal component analysis, unbiased flow cytometry analysis (using CITRIS), chi-square automatic interaction detection (CHAID), a decision tree technique, to predict disease outcome (over 9-33 months post diagnosis), and individual cell types comparisons.

Results

Using these standard and unbiased approaches, we identified several acute infection biomarkers that distinguish those patients that will resolve infection from those that develop chronic disease. We identified significant differences in Th17 and Th17/T regulatory (Treg) ratios, but not in Th1 frequencies or total numbers based on disease outcome. Patients with chronic disease had lower Th17 and higher Treg frequencies than patients that resolved disease.

Conclusion

The inability to resolve *coccidioides* infection may be a result of reduced Th17 responses and elevated Treg frequency.

COCCIDIOIDOMYCOSIS ENDEMIC CHANNEL IN MEXICO (2000–2014)

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Introduction

Coccidioidomycosis in Mexico is a neglected infection because it is not mandatory to report diagnosed cases. It is believed that there is an underreporting because of this. The infection is restricted to arid regions, characteristic of northern Mexico, bordering to California, Arizona, New Mexico and Texas, considered the highest endemic areas in the United States. Endemic channels are a measure that allows to estimate a trend of cases through the distribution of frequencies over time. The number of cases are plotted and the areas are interpreted according to the upper (epidemic threshold) and lower (safety level) limits, delimited by quartiles 3 and 1. Quartile 2 is interpreted as an alert zone. The aim of this study was to develop an endemic channel to establish the trend of coccidioidomycosis in Mexico.

Methods

By consulting the dynamic cubes tool of the Secretariat of Health information system, cases of coccidioidomycosis were identified in Mexico between 2000 and 2014, an endemic channel was estimated using the quartile method. Data were plotted with Excel (Microsoft) and the incidence of cases were determined from January to December for each year.

Results

Sonora and Baja California were the states in Mexico with the highest incidence of coccidioidomycosis, and the endemic channel shows that January, February and June have the highest incidence of cases diagnosed from 2000 to 2014.

Conclusion

Endemic channels are useful as a surveillance tool to identify the excess of expected cases of a disease over time and recognize their seasonal patterns.

RAPID DETECTION OF *COCCIDIOIDES POSADASII* FROM A DEEP INFECTION USING A PLASMA-BASED NEXT-GENERATION SEQUENCING TEST

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Introduction

The diagnosis of invasive fungal infections in immunocompromised patients is challenging because of the breadth of potential pathogens and the limitations of available diagnostic technologies. We describe the rapid detection of *Coccidioides posadasii* in a hematopoietic stem cell transplant (HSCT) patient with miliary pneumonia and pyomyositis using a plasma-based next-generation sequencing (NGS) test.

Case

A 9-year old male from Mexico with history of pre-B-cell ALL and HSCT in 2015 was admitted in April 2017 with fevers, nonproductive cough, and bilateral lower extremity pain. His pre-HSCT course was complicated by diffuse multinodular lung densities and discrete nodules on his legs attributed to *Histoplasma capsulatum* based on histopathology. Fungal cultures, serology, and antigen testing were negative. The patient was treated with amphotericin B for 2 weeks, followed by itraconazole for 12 weeks, with resolution of the pulmonary and leg nodules.

On admission, the patient was empirically treated with cefepime and posaconazole. Chest CT revealed diffuse miliary lung disease, and MRI of his legs showed microabscesses in multiple muscle groups. Blood cultures, interferon-gamma release assay, PPD skin test, *Coccidioides* antibody, *Cryptococcus* antigen, and *Histoplasma* urine antigen were negative. Beta-D-glucan was positive at 325 pg/mL. Bronchoscopy was performed, and BAL culture grew anaerobic bacteria and normal respiratory flora. BAL AFB smear was negative. Given the lack of a specific etiology, a plasma sample was obtained for NGS testing.

Methods

The plasma sample was sent to Karius, Inc. (Redwood City, CA) for a plasma NGS test developed to detect cell-free pathogen DNA. DNA was extracted, libraries prepared and diagnostic NGS applied. Human DNA sequences were removed and pathogen reads were aligned against a reference-sequence database with a reportable range of over 1,250 bacteria, fungi, protozoa and viruses. Organisms present at a significance level above a predefined threshold were reported.

Results

Within 48 hours of sample receipt, plasma NGS test detected *C. posadasii*. Posaconazole was continued, and the patient clinically improved. Eleven days after sample collection, the BAL fungal culture grew presumptive *Coccidioides* species, which was confirmed two weeks later as *C. posadasii* by DNA PCR at the San Diego County Public Health Laboratory.

Conclusion

This novel plasma-based NGS test detected *C. posadasii* in an immunocompromised patient with miliary pneumonia and pyomyositis within a clinically-actionable timeframe. The result obviated the need for additional diagnostic evaluation and informed the targeting of antimicrobial therapy. This plasma NGS test is a promising tool for the rapid detection of fastidious organisms, particularly in immunocompromised patients susceptible to a broad range of potential pathogens.

MULTICENTER CLINICAL VALIDATION OF A CARTRIDGE-BASED REAL-TIME PCR SYSTEM FOR DETECTION OF *COCCIDIOIDES SPP.* IN LOWER RESPIRATORY SPECIMENS

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Introduction Available methods for diagnosis of coccidioidomycosis have significant shortcomings relative to accuracy and timeliness. These shortcomings lead to missed diagnosis or misdiagnosis resulting in ineffective use of antimicrobial agents for extended periods, as well as increased morbidity and mortality. We used retrospective and prospective samples to evaluate the diagnostic performance and reproducibility of a new cartridge-based real-time PCR assay for *Coccidioides spp*. (GeneSTAT® *Coccidioides* Assay; DxNA LLC, St. George, UT) directly in bronchoalveolar lavage (BAL) and bronchial washing (BW) specimens and compared them to today's gold standard fungal culture.

Methods The GeneSTAT *Coccidioides* Assay uses a 106-bp sequence target that is repeated multiple times (~60X) within a genus-specific transposon genome of *C. posadasii* and *C. immitis*. This increases the amount of target DNA available per organism and thus lowering the limit of detection (LOD) for extracted DNA to 10 genome equivalents/mL. The system's sensitivity was measured using 51 retrospective (stored at -70 °C) and 4 prospective (maintained at 4 °C) culture positive BAL/BW samples. The systems specificity was measured using 49 retrospective and 228 prospective culture negative BAL/BW samples. A total of 332 prospective and retrospective individual patient specimens were tested by the GeneSTAT *Coccidioides* Assay across three clinical test sites. Assay reproducibility was measured across the 3 test sites by testing a panel of BAL samples that had been spiked with different concentrations of *C. posadasii* spherules (0X, 1X, and 3X LOD).

Results Retrospective sample sensitivity was 100% across the three sites and specificity ranged between 93.8% and 100%. There was little variance in the percent agreement across the three sites, 95.6% - 100%. Additionally, a total of 232 fresh (prospective) de-identified BAL/BW specimens were tested across the three clinical sites, which included a number of specimens from Southern California to provide a diversity of isolates. Specimens were tested by fungal culture with any isolates of *Coccidioides* being confirmed by molecular means (Accuprobe®). Sensitivity of the GeneSTAT *Coccidioides* Assay across the three sites was 100% (4/4) for fresh specimens and overall specificity of the assay was 99.6% (227/228), ranging from 98.0% to 100%.

Conclusion The GeneSTAT *Coccidioides* Assay performed on the GeneSTAT instrument was a sensitive and specific diagnostic test when compared to fungal culture and the 100% level of reproducibility across multiple operators at multiple sites confirmed its robustness.
Note: This study was supported by DxNA LLC, St. George, UT, as part of an FDA submission for 501(k) clearance.

Lipid components of *Coccidioides* parasitic cells suppress host immune response to Coccidioidomycosis

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Introduction

Coccidioides is a dimorphic fungus and causative agent of coccidioidomycosis, a human respiratory disease endemic to the Americas. After inhalation, arthroconidia undergo isotropic growth in the lungs and convert into multinucleate parasitic cells (spherules). A process of cytoplasmic segmentation then leads to the differentiation of hundreds of endospores. The spherule outer wall (SOW) is a membranous layer that is shed *in vivo* during parasitic cell maturation and has been shown to be lipid-rich. A dominant glycoprotein (SOWgp) associated with the SOW plays a role in immunogenicity and virulence of *Coccidioides*. However, a genetically-engineered mutant strain which lacks expression of SOWgp was shown to retain immunogenicity of its isolated, outer wall layer. The aim of our study was the characterization of lipids extracted from SOW derived from the wild type and Δ*sowGP* strains.

Methods

The Soxhlet method was employed for separation of lipid components, and Nuclear Magnetic Resonance (NMR) Analysis was used to characterize acylglycerols and sphingolipids. High performance liquid chromatography/mass spectrometry (HPLC/MS) studies characterized sphingolipids. Immunoelectrophoresis was used to characterized the IgG subtypes.

Results

We showed that 60% of the SOW by weight is composed of lipids, including triglycerides, phospholipids and sphingolipids. NMR analysis revealed that monosaccharide- and disaccharide-linked acylglycerols and sphingolipids are present. The major fatty acid components of SOW lipids are myristic acid (C14:0), palmitic acid (C16:0), elaidic acid (C18:1n9t), oleic acid (C18:1n9c), and stearic acid (C18:0). SOW lipids are enriched with unsaturated fatty acids. The molecular masses obtained from HPLC/MS studies confirmed that the major sphingolipids are sphingosin and ceramide types. We found that patients with coccidioidomycosis have higher titers of IgG1, IgG3 and IgE against SOW lipids compared to healthy individuals. We also observed that peripheral mononuclear cells obtained from both healthy donors and coccidioidomycosis patients produced less TNFα in the presence of SOW lipids. Neutrophils derived from C57BL/6 and DBA/2 mice incubated with SOW lipids revealed a significant reduction in their fungicidal activity against *Coccidioides* arthroconidias. The lipids had no effect on viability of the host cells. Furthermore, we showed that C57BL/6 mice that were subcutaneously challenged with *Coccidioides* spores in the presence of SOW lipids had disseminated disease.

Conclusion

Comparative compositional analyses of SOW derived from the wild type and Δ*sowGP* mutant strains revealed that the same components are present in the two fractions, but were quantitatively lower in the mutant strain. SOW lipids play a role in immunomodulation of the host inflammatory response to *Coccidioides* infection.

COCCIDIOIDOMYCOSIS IN CHILDREN YOUNGER THAN TWO YEARS OF AGE: A RETROSPECTIVE REVIEW

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Introduction

Coccidioidomycosis, a disease endemic to the southwestern United States, is associated with significant morbidity, especially in patients in the extremes of age and patients with immunodeficiency and other comorbidities. This review aims to study the disease burden in infants and young children.

Methods

Retrospective review of coccidioidomycosis cases were retrospectively reviewed in patients younger than two years of age seen at Valley Children's Hospital between 1/1/07 and 12/31/16.

Results

Thirty one cases were identified. Median age was 12 months (IQR, 5.2- 16.1); majority were males (61%), Hispanic (81%) and without comorbid conditions (90%). Fever and cough were the most common symptoms occurring in 87% and 84% of the cases respectively; Erythema nodosum was seen in only 13% of the patients. 55% of the patients had disseminated disease, while 45% had pulmonary disease alone. The most commonly involved extra-pulmonary sites were: mediastinum (29%), central nervous system (10%), larynx (10%), bone (6%), and skin (6%). Majority of patients received antifungal therapy (97%), with 58% of them requiring two or more drugs. Patients with disseminated disease presented at a younger age than those with pulmonary disease alone (9.2 vs. 14.2 months, P=0.02); had higher peak coccidioidal complement fixation titers (median 1:64 vs. 1:32, P=0.04); and required longer duration of therapy (median 746 vs. 296 days, P=0.002); more frequently with combination antifungal therapy (94% vs 15%, P=0.0001). Majority of the cases (74%) required hospitalization.
In regards to outcome, disease resolution was achieved in 87% of the cases; 6.5 % had active but stable disease on maintenance therapy; and 6.5 % experienced a relapse. No deaths occurred in this cohort.

Conclusion

Coccidioidomycosis in children younger than two years of age is associated with significant morbidity and health care utilization. Disseminated disease is frequently encountered in this age group and should be considered when formulating the plan for treatment and diagnostic investigations.

ACKNOWLEDGEMENTS

2017 Cocci Study Group 60th Annual Meeting Hosts
In Coordination with the 7th International Coccidioidomycosis Symposium
August 10-13, 2017, Stanford University

Course Directors
Neil M. Ampel
Stan Deresinski

Course Planners
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Annual Meetings of the Coccidioidomycosis Study Group

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

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

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

Important Internet Web Sites

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

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

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

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

- **Valley Fever Americas Foundation**

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