IDCases 23 (2021) e01049

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcr

Case report

Fatal coccidioidomycosis involving the lungs, brain, tongue, and adrenals in a cirrhotic patient. An autopsy case

David Chee[a], August W. Moritz[b], Amanda P. Profit[c], Apeksha N. Agarwal[d], Gregory M. Anstead[e,f,*]

[a] San Antonio Infectious Diseases Consultants, 8042 Wurzbach Road, San Antonio, TX, 78229, United States
[b] Methodist Hospital, 7700 Floyd Curl, San Antonio, TX, 78229, United States
[c] Medical City Dallas Hospital, 7777 Forest Ln, Suite A-200, Dallas, TX, 75230, United States
[d] Department of Pathology, University of Texas Health, 7703 Floyd Curl Drive, San Antonio, TX, 78229, United States
[e] Medical Service, Division of Infectious Diseases, South Texas Veterans Healthcare System, 7400 Merton Minter Blvd, San Antonio, TX, 78229, United States
[f] Department of Medicine, Division of Infectious Diseases, University of Texas Health, 7703 Floyd Curl Dr, San Antonio, TX, 78229, United States

ARTICLE INFO

Article history:
Received 2 December 2020
Accepted 12 January 2021

Keywords:
Coccidioidomycosis
Tongue
Lungs
Brain
Adrenals
Cirrhosis
Autopsy

ABSTRACT

In this paper, we describe a case of fatal disseminated coccidioidomycosis (CM). The patient was a 44-year old male with a history of cirrhosis who presented with altered mental status, cough, and an enlarged, ulcerated tongue. On evaluation, the patient was found to have coccidioidal infection of the tongue, lungs, and brain. Despite over two months of antifungal treatment, the patient died from aspiration pneumonia and at autopsy was found to have persistent infection of the tongue and lungs, extensive mycosis of the brain, and involvement of both adrenal glands. The fulminant course of coccidioidomycosis in this patient is ascribed to his baseline cirrhosis and lymphocytopenia. There are few autopsy cases of CM that have been described in the post-antifungal era and few published cases of CM with either tongue or adrenal involvement.

Introduction

Coccidioidomycosis (CM) is caused by dimorphic fungi of the genus *Coccidioides (C. immitis* (mostly California isolates) and *C. posadasii* (other areas)). It typically presents as acute and chronic pulmonary disease. However, the infection may disseminate widely, especially to cutaneous, osseous, and central nervous system sites. Coccidioidomycosis is a significant health problem in the southwestern USA and Latin America, with 150,000 cases of acute infections occurring annually in the United States alone [1,2]. About 1 % of CM cases result in dissemination, and one third of these cases are fatal [2].

The aim of the current study is to report a fatal case of disseminated CM. The patient had a history of cirrhosis and presented with altered mental status, cough, and an enlarged, ulcerated tongue. A computerized tomograph of the chest indicated an active granulomatous process and the patient had positive *Coccidioides* serologic tests of the serum and cerebrospinal fluid. A subsequent biopsy revealed that the patient had coccidioidal infection of the tongue, in addition to the lungs and the brain.

Despite over two months of antifungal treatment, the patient died and, at autopsy, was found to have persistent infection of the tongue and lungs, extensive involvement of the brain, and infection of both adrenal glands. There are few autopsy cases of CM that have been described in the post-antifungal era and few published reports of CM with either tongue or adrenal infection. In addition, previous cases of CM involving the tongue or the adrenal gland were reviewed.

Methodology

To find cases of CM that involved either the tongue or the adrenal gland, PubMed was searched for articles using the terms "*Coccidioides* and tongue" and "*Coccidioides* and adrenal." Additional references were obtained by bibliographic branching and Google Scholar searches with identical search terms. These databases were searched for autopsy cases of CM in a similar manner. References published in English, German, and Spanish were examined.

* Corresponding author at: Medical Service, Division of Infectious Diseases, South Texas Veterans Healthcare System, 7400 Merton Minter Blvd, San Antonio, TX, 78229, United States.
E-mail addresses: chee@saidc.com (D. Chee), August.Moritz@mhshealth.com (A.W. Moritz), draprofit@gmail.com (A.P. Profit), AgarwalA@uthscsa.edu (A.N. Agarwal), anstead@uthscsa.edu (G.M. Anstead).

http://dx.doi.org/10.1016/j.idcr.2021.e01049

Case

A 44-year old Hispanic man presented with an enlarged tongue with a dorsal ulcer and he was referred to the otolaryngology service to obtain a biopsy. He reported a cough, dyspnea on exertion, hemoptysis, epistaxis, a painful tongue, and odynophagia for about one month, resulting in an 11-kg weight loss. The patient reported confusion and speech dysfluency for the last two weeks. He denied fevers, chills, night sweats, nausea, vomiting, or diarrhea. The patient was noted to have jaundice and was hospitalized for suspected hepatic encephalopathy. The patient's past medical history included intravenous drug abuse and alcoholic and hepatitis C cirrhosis, with a transjugular intrahepatic porto-systemic shunt in place. The patient was an inmate at a state prison in south central Texas. Previously, he had been a truck driver with travel in Mexico and California. On admission, vital signs were a temperature of 36.9 °C, pulse 95, blood pressure 109/65 mm Hg, respiration rate 19 per minute, with an oxygen saturation of 96 % on room air. The patient was jaundiced; he was alert, but oriented only to self and place. His speech was hoarse and dysfluent. The nares were crusted with dried blood. His tongue was swollen, with dorsal and lateral ulcers with greenish exudate. He also had a shallow ulcer of the right buccal mucosa (Fig. 1A and B). Splenomegaly and palpable purpura of the legs were apparent. The remainder of the physical exam was normal. Routine laboratory tests were remarkable for an elevated bilirubin level (9.3 mg/dL; reference range (RR) 0.2–1.2 mg/dL), hypoalbuminemia (2.0 g/dL; RR 3.2–5.0 g/dL), thrombocytopenia (platelets 65 K/μL, RR 140−377 K/μL), coagulopathy (International Normalized Ratio 2.0 (RR 0.8–1.2), and lymphocytopenia (360/μL; RR 900−3100 K/μL). Thyroid function tests and an ammonia level were within normal limits. A human immunodeficiency virus serologic test was negative. A computerized tomograph of the chest revealed a tree-in-bud pattern and diffuse bronchial wall thickening (Fig. 2). A lumbar puncture found clear cerebrospinal fluid (CSF) with 59 WBC/μL (RR 0–5 WBC/μL) with a differential of 13 % segmented cells, 52 % lymphocytes, and 35 % monocytes. The CSF glucose level was low at 24 mg/dL (RR 45−80 mg/dL) and the protein level was elevated at 295 mg/dL (RR < 45 mg/dL).

Coccidioides IgM and IgG titers were positive in the serum at 2.8 (RR ≤ 0.9) and 13.3 (RR ≤ 0.9), respectively; immunodiffusion and complement fixation in the serum and CSF were positive but <1:2. The *Coccidioides* IgG was positive in the CSF, but IgM was negative. Fungal cultures of the sputum grew a white cottony mold that was DNA probe positive for *Coccidioides* species.

The patient was started on high-dose fluconazole (initially 800 mg/day, later increased to 1600 mg per day). On hospital day-7, a tongue biopsy was performed that showed *Coccidioides* spherules. The patient's pulmonary symptoms improved over several weeks, however, the enlargement of the tongue did not appreciably regress and the lingual ulcer did not heal. Furthermore, his mental status did not improve. An initial CT scan revealed an old lacunar infarct in the anterior thalamus and enlarged bilateral temporal horns consistent with hydrocephalus. A brain MRI revealed an ischemic event within the corpus callosum. Due to concern about coccidioidal central nervous system vasculitis, the patient was given dexamethasone 6 mg IV twice a day for 7 days, followed by 3 mg IV each day for 7 days. On hospital day-22, his platelet count dropped to 8 K/μL. Antifungal therapy was changed to liposomal amphotericin (5 mg/kg) due to concern that high-dose fluconazole was exacerbating thrombocytopenia and within six days the platelet count improved to 30 K/μL.

On hospital day-29 he had an aspiration event with hypoxemia, hypotension, and depressed mental status that required intubation and pressor therapy. After 5-days, the patient was able to be extubated. By hospital day-36, the tongue had regressed in size, but the patient still had difficulty swallowing and failed a swallowing study. On day-43, liposomal amphotericin was stopped and fluconazole 400 mg orally each day was started, but was increased to 800 mg IV each day due to increased tongue pain. On hospital day-63, patient was noted to have tachypnea, tachycardia, hypoxemia (oxygen saturation 88–90 % on room air), an elevated troponin level, and electrocardiographic changes indicative of a myocardial infarction. A new right upper lobe consolidation on chest X-ray suggested that aspiration had occurred again. The

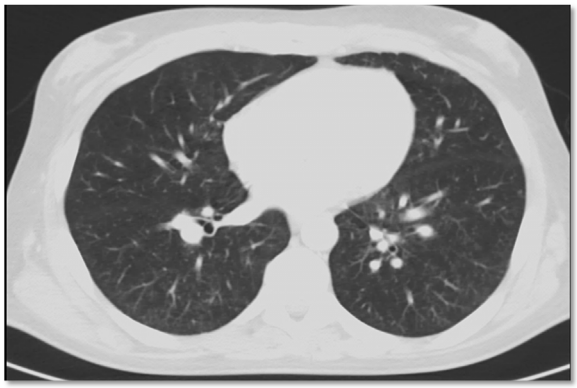

Fig. 2. Computerized tomograph of the chest showing tree-in-bud pattern indicative of bronchiolar obstruction.

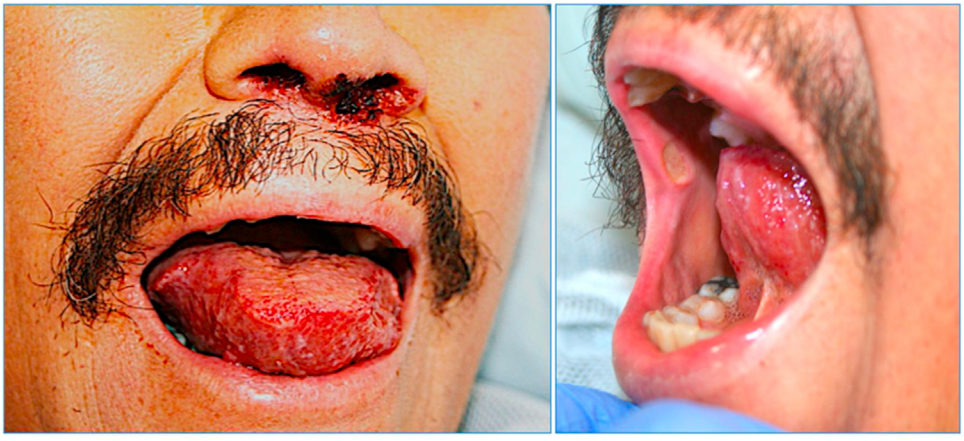

Fig. 1. Photographs of the case patient showing: A (left) enlargement of the tongue and blood-encrusted nares; B (right), ulcer of the right buccal mucosa.

patient's family decided to transition him to comfort care and he expired. An autopsy was performed.

Autopsy findings

Tongue

Multiple tongue ulcers were present. Representative sections of the tongue revealed chronic inflammation and multinucleated giant cells with observable round fungal organisms consistent with coccidioidomycosis (Fig. 3).

Lungs

The lungs were edematous, with weights of 1240 and 995 g for the right and left lungs, respectively, compared to the average weight range of the male right and left lungs of 155–720 g and 112–675 g, respectively [3]. The bronchi contained yellow-brown frothy fluid. The cut surfaces of the lungs revealed diffusely edematous brown-red parenchyma. Representative sections of the lungs showed dilated vasculature and multiple foci of giant cells and lymphocytes with fungi consistent with *Coccidioides* (Fig. 4). The alveoli were diffusely filled with edema fluid as well as acute and chronic inflammatory cells. The pleural surfaces contain adhesions to the pericardium on the right and dense circumferential adhesions to the left chest wall.

Brain

The remarkable gross features of the brain were bilateral tonsillar herniation and dilatation of the ventricles consistent with hydrocephalus. There were small cavities (1.0 × 1.5 cm and 0.5 × 0.5 cm) present within the left anterior and posterior putamens (the outermost portions of the basal ganglia), respectively. Microscopically, sections of the cerebral cortex, basal ganglia, hippocampus, cerebellum, midbrain, midpons, and medulla revealed multiple foci of coccidioidal spherules, interspersed with chronic inflammatory cells (Fig. 5). Section of the left basal ganglia showed an infarction in the phase of resorption. There was diffuse neuronal loss within the CA1 area of Ammon's horn of the hippocampus (an area important for memory formation) [4].

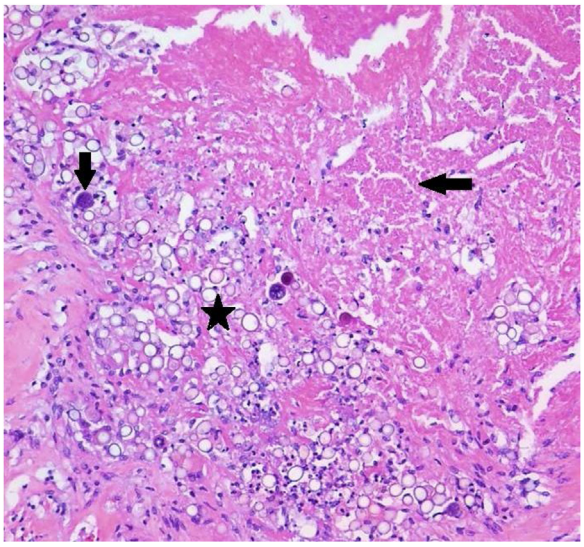

Fig. 4. Section of the lung showing necrosis (left-pointing arrow) with abundant thick-walled spherules of *Coccidioides* (star), some containing endospores (down arrow) surrounded by histiocytes (H&E, x200).

Adrenals

Grossly, the adrenal glands displayed their usual shape and the cut surfaces displayed a normal distribution of cortex and medulla bilaterally. Microscopically, sections of both adrenal glands revealed multinucleated giant cells, lymphocytic infiltration, and observable fungi consistent with *Coccidioides* (Fig. 6).

Liver

The liver was diffusely nodular with multiple focal areas of opaque, raised yellow-tan patches. The cut surface displayed a "nutmeg" pattern congestion. Microscopically, representative

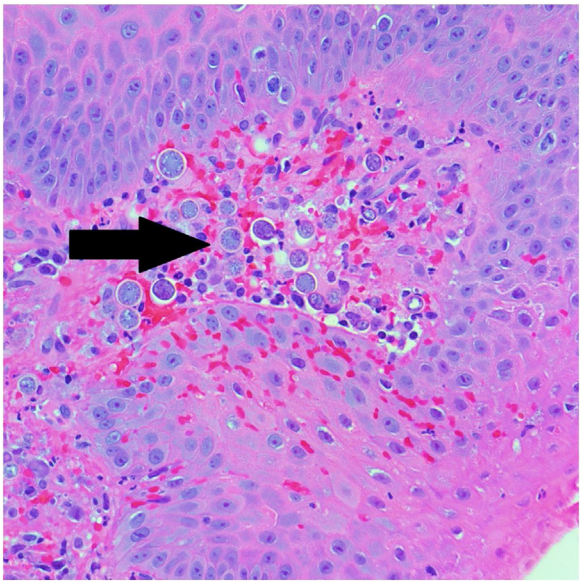

Fig. 3. Section of the tongue showing squamous mucosa with thick-walled spherules (arrow) of *Coccidioides* in the lamina propria (Hematoxylin and Eosin stain (H&E), x200).

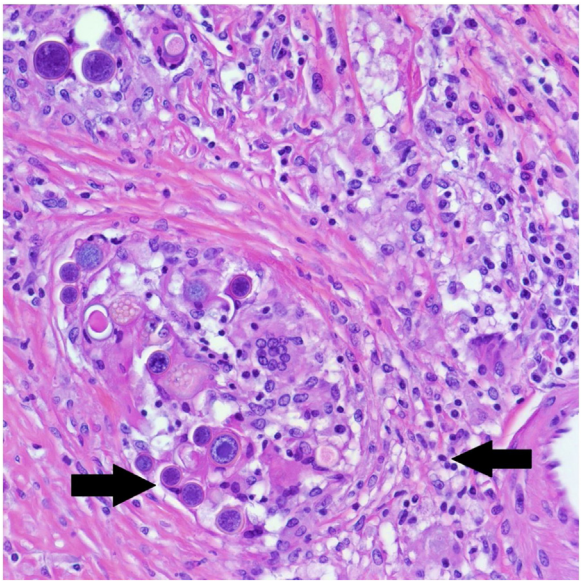

Fig. 5. Photomicrograph of a section of the brain showing spherules of *Coccidioides* (right-pointing arrow) surrounded by chronic inflammatory cells (left-pointing arrow), including lymphocytes and plasma cells (H&E, ×400).

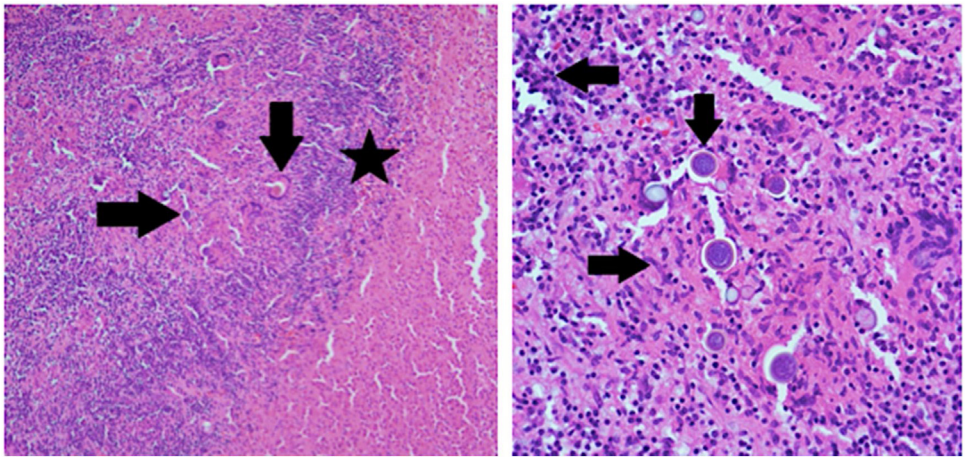

Fig. 6. Photomicrographs of sections of the adrenal gland showing: A (left), spherules of *Coccidioides* (right-pointing arrow), multinucleated giant cells (down arrow) and marked chronic inflammation (star) (H&E x100); B (right), spherules of *C. immitis* (down arrow), histiocytes (right-pointing arrow) and chronic inflammatory cells (left-pointing arrow) (H&E, x400).

Table 1
Cases of coccidioidomycosis of the tongue.

Case #; age, sex, [ref], year	Patient description; Location	Brief Clinical Course
1; [9], 1999	Argentina	No case details provided
2; 56, M, [5], 2005	Mexican farm worker in California; diabetes	Pt reported biting his tongue, then tongue enlarged and ulcerated over 1-mo; followed by progressive swelling and malodorous drainage, pain, dysphagia; negative CT scan of the chest, neck, and sinuses; tongue biopsy showed reactive squamous epithelium, granulation tissue, acute inflammation, and necrosis; positive IgG; treated with itraconazole for 1 month; resolution.
3; 51, F, [6], 2013	German traveler to Arizona	Presented with painless thickening of tongue; underwent tongue biopsy, which revealed granulomatous changes and numerous spherules; Chest CT showed hilar lymphadenopathy with streaky infiltrates and nodules. A gene probe of transbronchial biopsy specimen found *C. posadasii*. Treated with itraconazole 200 mg/day for 6 mos; resolution.
4; 60, M, [7], 2017	healthy; rural Mexico	Presented with ulcerated lesion of the tongue, growing for 5 mos. Biopsy of tongue showed granulomata with spherules. CXR: pulmonary lesions. Received itraconazole for six mos; due to liver function test elevation, itraconazole held for 1 mo; then resumed to complete 1 yr of treatment.
5; 34, M, [8], 2019	AIDS (CD4 39 cells/mm^3); HIV viral load 197,000 copies/mL); Arizona	Presented w/ a 1-wk history of headache, fever, confusion and large, ulcerative lesion of tongue; CXR bilateral patchy infiltrates; positive *Coccidioides* IgG in blood/CSF. Biopsy of tongue lesion revealed spherules. *Coccidioides* grew from bronchoalveolar lavage. Received liposomal amphotericin B and fluconazole for 2 wks, followed by fluconazole monotherapy. HIV genotype revealed resistance to one of the patient's medications; antiretrovirals adjusted. At 3 mos after presentation, fever and headache resolved, tongue lesion decreased in size, and HIV viral load undetectable. Lost to follow-up.

AIDS, acquired immunodeficiency syndrome; CT, computerized tomography; CXR, chest x-ray.

sections of the liver displayed centrilobular congestion, lobular disarray, multiple regenerative nodules, and dense bridging fibrosis indicative of cirrhosis.

Other organs

Microscopic examination of the heart, esophagus, intestines, gall bladder, pancreas, kidneys, urinary tract, spleen, pituitary and paratracheal lymph nodes showed no evidence of fungal invasion.

Discussion

The patient had *Coccidioides* infection in two unusual body sites, the tongue and the adrenal gland. Furthermore, the patient had extensive coccidioidal involvement of the brain and the lungs, despite prolonged antifungal treatment. Coccidioidomycosis of the tongue is rare with only five other cases in the medical literature (Table 1). In these five cases, Case **2** may have been a primary infection, arising from inoculation of a prior tongue lesion with *Coccidioides* sp., likely by oral dust exposure (the patient was a farm worker) [5]. In Cases **3** and **4**, CM of the tongue was observed in conjunction with pulmonary CM [6,7], and in Case **5**, tongue involvement occurred in the setting of advanced Acquired Immunodeficiency Syndrome, with concurrent pulmonary and CNS involvement [8]. The involvement of the tongue in the illness of the patient described herein is more than just a curiosity; it is likely contributed to the aspiration events, which ultimately led to the patient's death.

Although CM is a so-called "great imitator" disease that can involve almost any organ of the body, reports of involvement of the adrenal glands are rare in the post-antifungal era (after the introduction of amphotericin B in 1957 [10]), with only five other reported cases (Table 2, Cases **8-12**). This is in contrast to several other systemic mycoses, such as histoplasmosis [11], cryptococcosis [12], blastomycosis [13], and especially paracoccidioidomycosis (in which adrenal involvement occurs in 90 % of cases) [14,15].

Table 2
Cases of Adrenal Coccidioidomycosis.

Case #; age, sex, ref; year	Patient description, Location	Brief Clinical Course
6; 62, M; [22]; 1952	Railroad worker, Arizona	Presented w/ arthritis of knee/wrist and hyperpigmentation; specimen from wrist grew *Coccidioides*. Developed hypotension; given adrenal cortex extracts, but died. Autopsy showed pulmonary CM and markedly enlarged adrenals ((total wt 165 g)(normal wt 4 g)). Normal adrenal tissue replaced by caseating necrosis, granulation, and fibrosis. Many multinucleated giant cells at the periphery of the necrotic areas, some containing spherules.
7; 44, M, [22]; 1952	farm worker, California	Presented w/ weakness, nausea/vomiting. CXR: bilat infiltrates. PMH of CM for 12 yrs. Over months, skin became darker, and patient became weak, confused, emaciated, and hypotensive. Received cortisone and adrenal cortex extract, but died in a few days. Autopsy showed enlarged adrenal glands (total wt 20-g). Numerous granulomata, nearly replaced both adrenals, and involved the lungs, thoracic lymph nodes, spleen, and meninges; spherules present.
8; 37, M, [23**]**; 1978	Resident of Los Angeles, CA	History of traumatic brain injury. Suffered cognitive decline and headaches over 4 yrs. Presented with fever, weakness, arthalgias, skin lesions, and photophobia. Diagnosed with a viral syndrome. Returned in 6 weeks with fever, severe headache, dysarthria, and hemiparesis. Lumbar puncture showed pleocytosis and elevated protein. No improvement with penicillin, chloramphenicol, and corticosteroids and the patient lapsed into a semi-comatose state. A biopsy of the skin lesions revealed *Coccidioides*. Started on amphotericin B but expired in 5-days. At autopsy, coccidioidal granulomata were found in the eyes, lungs, skin, brain, heart, pancreas, liver, adrenals, and prostate.
9; 48, M, [24]; 1996	healthy traveler, in Sweden	Presented with RUQ abdominal pain. Ultrasound showed bilateral adrenal tumors, 7 cm. Elevated plasma ACTH and renin activity. Adrenal biopsy showed spherical fungi; serologic investigation consistent with CM. Treated with cortisone and fluconazole. Poor serologic response to 3-mo Rx of fluconazole and received course of amphotericin B, but stopped due to renal insufficiency. Completed 10-mos of fluconazole with serologic response, but adrenal lesions did not regress radiographically.
10; 45, F; [25]; 1999	farm worker from TX, in North Dakota	Pt with menorrhagia; underwent hysterectomy and salpingo-oophorectomy. A resected colon abscess showed caseating granulomas; culture positive for *Coccidioides*. Infiltrates on CXR. Started fluconazole. Subsequently developed hyperpigmentation/hyponatremia. Had elevated ACTH. Treated with prednisone, fludrocortisone. Continued fluconazole; improved at 5 mos and then lost to follow-up. Adrenal CM assumed.
11; 55, M, [26]; 2017	smoker; Arizona	Presented w/ 2 mos of increasing fatigue. Chest CT showed RUL nodule; PET scan revealed same nodule and L adrenal mass. Biopsy of lung lesion revealed necrotizing granulomas with spherules. Adrenal biopsy inconclusive. Received fluconazole and lung and adrenal lesions regressed.
12; adult M, unspecified age, [27]; 2019	Diabetes mellitus, smoker; Mexico	Presented with weight loss, confusion, dysfluency, headache, respiratory distress. CXR with miliary pattern. Lumbar puncture suggested tuberculosis; started on TB therapy and amphotericin B. Pt had pneumothorax and died of cardiopulmonary arrest. An autopsy showed granulomas with spherules in the lungs, thoracic lymph nodes, liver, spleen, thyroid, kidneys, meninges. L adrenal gland contained a coccidioma, 4 × 3 × 3 cm, composed of granulomas, caseous necrosis, and multiple spherules.

Abbreviations: ACTH, adrenocorticotrophic hormone; CXR, chest X-ray; RUL, right upper lobe.

However, even in paracoccidioidomycosis, symptomatic adrenal insufficiency occurs in only about 7 % of cases [16]. There is no satisfactory explanation for the specific tropism of fungal pathogens like *Paracoccidioideslutzii* for the adrenal glands and the uncommon adrenal involvement in *Coccidioides* infection, even though the two fungi are related phylogenetically (both genera are in the order Onygenales) [17].

However, in the pre-antifungal era, CM of the adrenal gland was seen in autopsy series and in untreated cases of long-duration (Table 2, cases **6** and **7**). In a series of 50 autopsy cases conducted in the pre-antifungal era, adrenal involvement was seen in 16 patients; in none of the cases were the adrenals completely destroyed, but in a number of patients both adrenals were infected. The adrenal lesions usually consisted of one or more granulomatous nodules, with no apparent adrenal insufficiency. Based on this autopsy series, the order of frequency of organ involvement in disseminated CM was: lungs, lymph nodes, spleen, skin and subcutaneous tissues, liver, kidney, bones, meninges, adrenals, myocardium, brain, pericardium, and pancreas, with other tissues having only incidental involvement [18]. In an autopsy series of 36 CM patients from 1945, one case of adrenal involvement with Addison's disease was noted [19]. In an autopsy series of 131 CM patients, conducted from 1947 through 1965, found 22 cases of adrenal involvement (16.8 %); no cases of adrenal insufficiency were observed [20]. However, in another autopsy series of 18 patients from 1929, no adrenal involvement was observed [21].

Table 2 shows seven cases of CM with adrenal involvement [22–27]. The adrenals have significant functional reserve; the typical clinical picture of Addison's disease only arises if less than 5% of intact residual adrenal tissue remains [22]. Nevertheless, Cases **6**, **7**, **9**, and **10** did display adrenal insufficiency [22,24,25]. In Cases **8** and **12**, the diagnosis and treatment of CM was likely delayed, allowing for extensive dissemination [23,27]. Case **9** is unusual in the that adrenals were the only evident site of coccidioidal involvement [24]. In our case, the "adrenal hyperplasia" reported as the initial CT report was not recognized as CM of the adrenal gland during the patient's hospital course, because he displayed no

clinical manifestations of adrenal insufficiency, despite the advanced stage of the disease in the lungs and brain.

The most common central nervous system presentation of CM is basilar meningitis, which is observed in nearly 50 % of cases of disseminated CM [28]. Other central nervous system complications of CM include hydrocephalus, vasculitic infarction, mass lesions, abscesses, cranial neuropathy, and arachnoiditis. Approximately 40 % of coccidioidal meningitis patients will present with or acquire hydrocephalus during the course of the infection. The frequency of vasculitic infarction based on radiographic studies indicate an incidence as high as 40 %. Clinical presentations of vasculitic infarction (e.g., aphasia, hemianopsia, hemiparesis) occur in about 10 % of meningitis cases [29]. In this patient, there were small cavities, 1.0 × 1.5 cm and 0.5 × 0.5 cm, present within the left anterior and posterior putamens (the outermost portions of the basal ganglia), respectively, indicative of prior infarction. Microscopically, the patient had widespread mycosis of the brain, with sections of the cerebral cortex, basal ganglia, hippocampus, cerebellum, midbrain, midpons, and medulla all affected.

This patient suffered a fulminant case of disseminated CM, despite prolonged antifungal therapy; his identified immunosuppressive condition was decompensated cirrhosis and lymphocytopenia. Cirrhosis alters the function of circulating immune cells and impairs the synthesis of innate immunity proteins (such as complement) and secreted pattern-recognition receptors (e.g., C-reactive protein, lipopolysaccharide-binding protein, and soluble CD14) [30,31]. Cirrhosis has been described as a risk factor for cryptococcosis [32], aspergillosis [31,33], and CM [34–38]. Blair and coworkers found that end-stage liver disease (ESLD) increased the risk of acquisition of CM by 100-fold, based on a group of ESLD patients living in a high-risk area (Arizona) awaiting liver transplantation [36].

Conclusions

Herein, we described a case of fatal disseminated coccidioidomycosis. The patient, a 44-year old male with cirrhosis, presented with altered mental status, cough, and an enlarged, ulcerated tongue. On evaluation, the patient was found to have coccidioidal infection of the tongue, lungs, and brain. Despite over two months of antifungal treatment, the patient died from aspiration pneumonia and at autopsy was found to have persistent infection of the tongue and lungs, extensive brain involvement, and bilateral adrenal infection. Tongue involvement is uncommon in coccidioidomycosis, and has been reported in only five other cases. Adrenal coccidioidomycosis was reported in autopsy series in the pre-antifungal era, but also has been uncommonly reported since the introduction of antifungal therapy. The fulminant course of coccidioidomycosis in this patient was ascribed to his baseline cirrhosis and lymphocytopenia.

References

[1] Laniado-Laborín R, Arathoon EG, Canteros C, Muñiz-Salazar R, Rendon A. Coccidioidomycosis in Latin America. Med Mycol 2019;57(Suppl. 1):S46–55, doi:http://dx.doi.org/10.1093/mmy/myy037.

[2] Odio CD, Marciano BE, Galgiani JN, Holland SM. Risk factors for disseminated coccidioidomycosis, United States. Emerg Infect Dis 2017;23:308–11, doi: http://dx.doi.org/10.3201/eid2302.160505.

[3] Molina DK, DiMaio VJ. Normal organ weights in men: part II-the brain, lungs, liver, spleen, and kidneys. Am J Forensic Pathol 2012;33:368–72, doi:http://dx.doi.org/10.1097/PAF.0b013e31823d29ad.

[4] Anand KS, Dhikav V. Hippocampus in health and disease: an overview. Ann Indian Acad Neurol 2012;15(4):239–46, doi:http://dx.doi.org/10.4103/0972-2327.104323.

[5] Rodriguez RA, Konia T. Coccidioidomycosis of the tongue. Arch Pathol Lab Med 2005;129:e4–6, doi:http://dx.doi.org/10.1043/1543-2165(2005)129<e4:COTT>2.0.CO.

[6] Stich A, Müller A, Tintelnot K. Coccidioidomycosis with manifestation on the tongue. Pathologe 2013;34:548–51, doi:http://dx.doi.org/10.1007/s00292-013-1834-6.

[7] Mendez LA, Flores SA, Martinez R, de Almeida OP. Ulcerated lesion of the tongue as manifestation of systemic coccidioidomycosis. Case Rep Med 2017;2017:1489501, doi:http://dx.doi.org/10.1155/2017/1489501.

[8] Myers RA, Zmarlicka MT. Disseminated coccidioidomycosis. New Eng J Med 2019;380:e44, doi:http://dx.doi.org/10.1056/NEJMicm1811100.

[9] Bava AJ, Negroni R, Arechavala AI, et al. Study of eight cases of coccidioidomycosis in a hospital of Buenos Aires. Rev Iberoam Micol 1999;16:111–3 PMID:18473580.

[10] Winn WA. Coccidioidomycosis and amphotericin B. Med Clin N Am 1963;47:1131–48 1963. PMID: 14065439.

[11] Wheat LJ. Histoplasmosis: a review for clinicians from nonendemic areas. Mycoses 2006;49:274–82, doi:http://dx.doi.org/10.1111/j.1439-0507.2006.01253.x.

[12] Hung Z-S, Lai Y-H, Hsu Y-H, et al. Disseminated cryptococcosis causes adrenal insufficiency. Intern Med (Tokyo) 2010;49:1023–6, doi:http://dx.doi.org/10.2169/internalmedicine.49.3051.

[13] Eberle DE, Evans RB, Johnson RH. Disseminated North American blastomycosis. Occurrence with clinical manifestations of adrenal insufficiency. JAMA 1977;238:2629–30, doi:http://dx.doi.org/10.1001/jama.238.24.2629.

[14] Tendrich M, Wanke B, Del Negro G, Wajchenberg B. Adrenocortical involvement in paracoccidioidomycosis. In: Franco M, Da Silva C, Restrepo A, Del Negro G, editors. Paracoccioidomycosis. Boca Raton, FL: CRC Press, Boca Raton; 1993. p. 303–10.

[15] Salfelder K, Doehnert G, Doehnert HR. Paracoccidioidomycosis; anatomic study with complete autopsies. Virchows Arch A Pathol Pathol Anat 1969;348:51–76 PMID: 5307685.

[16] Tobón AM, Agudelo CA, Villa CA, Quiceno W, Estrada S, et al. Adrenal function status in patients with paracoccidioidomycosis after prolonged post-therapy follow-up. Am J Trop Med Hyg 2010;83:111–4, doi:http://dx.doi.org/10.4269/ajtmh.2010.09-0634.

[17] Whiston E, Taylor JW. Comparative phylogenomics of pathogenic and nonpathogenic species. G3 (Bethesda) 2015;6:235–44, doi:http://dx.doi.org/10.1534/g3.115.022806.

[18] Forbus WD, Bestebreurtje AM. Coccidioidomycosis: study of 95 cases of disseminated type with special reference to pathogenesis of the disease. Mil Surg 1946;99:653–719 PMID: 20276803.

[19] Butt EM, Hoffman AM. Healed or arrested pulmonary coccidioidomycosis: correlation of coccidioidin skin tests with autopsy findings. Am J Pathol 1945;21:485–505 PMID: 19970822.

[20] Huntington RWJr, Waldmann WJ, Sargent JA, et al. Pathological and clinical observations in 142 cases of fatal coccidioidomycosis on necropsy. In: Ajello L, editor. Proceedings of the Second Coccidioidomycosis Symposium. . p. 143–67.

[21] Evans N, Ball HA. Coccidioidal granuloma, analysis of 50 cases. JAMA 1929;93:1881–5.

[22] Maloney PJ. Addison's disease due to chronic disseminated coccidioidomycosis. Arch Intern Med 1952;90(6):869–78, doi:http://dx.doi.org/10.1001/archinte.1952.00240120144012.

[23] Zakka KA, Foos RY, Brown WJ. Intraocular coccidioidomycosis. Survey Ophthalmol 1978;22:313–21, doi:http://dx.doi.org/10.1016/0039-6257(78)90176-5.

[24] Papadopoulos KI, Castor B, Klingspor L, Dejmek A, Lorén I, Bramnert M. Bilateral isolated adrenal coccidioidomycosis. J Intern Med 1996;239:275–8, doi:http://dx.doi.org/10.1046/j.1365-2796.1996.407760000.x.

[25] Chowfin A, Tight R. Female genital coccidioidomycosis (FGC), Addison's disease and sigmoid loop abscess due to *Coccidioides immitis*; case report and review of literature on FGC. Mycopathologia 1999;145:121–6, doi:http://dx.doi.org/10.1023/a:1007058106662.

[26] Chaddha U, Patil PD, English R, Walia R, Panchabhai TS. The imitation game: a 55-year-old man with a lung and adrenal mass. J Bronchology Interv Pulmonol 2017;24:e52–4, doi:http://dx.doi.org/10.1097/LBR.0000000000000397.

[27] Lazos-Ochoa M, Tovar-Echavarri M, Romero-Cabello R, Romero-Feregrino R. Disseminated coccidioidomycosis with giant coccidioidoma of the suprarenal gland. Autopsy case report. Rev Mex Patol Clin Med Lab 2019;66:20–6.

[28] Johnson RH, Einstein HE. Coccidioidal meningitis. Clin Infect Dis 2006;42:103–7, doi:http://dx.doi.org/10.1086/497596.

[29] Johnson R, Ho J, Fowler P, Heidari A. Coccidioidal meningitis: a review on diagnosis, treatment, and management of complications. Curr Neurol Neurosci Rep 2018;18(19), doi:http://dx.doi.org/10.1007/s11910-018-0824-8.

[30] Albillos A, Lario M, Alvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. J Hepatol 2014;61:1385–96, doi: http://dx.doi.org/10.1016/j.jhep.2014.08.010.

[31] Lipke AB, Mihas AA. Non-decompensated cirrhosis as a risk factor for invasive aspergillosis: a case report and review of the immune dysfunction of cirrhosis. Am J Med Sci 2007;334:314–6, doi:http://dx.doi.org/10.1097/MAJ.0b013e318068d79c.

[32] Albert-Braun S, Venema F, Bausch J, Hunfeld K-P, Schafer V. *Cryptococcus neoformans* peritonitis in a patient with alcoholic cirrhosis: case report and review of the literature. Infection 2005;33:282–8, doi:http://dx.doi.org/10.1007/s15010-005-4120-6.

[33] Lahmer T, Brandl A, Rasch S, et al. Prevalence and outcome of invasive pulmonary aspergillosis in critically ill patients with liver cirrhosis: an

observational study. Sci Rep 2019;9:11919, doi:http://dx.doi.org/10.1038/s41598-019-48183-4.
[34] Jenks JD, Reed SL, Hoenigl M. Risk factors and outcomes of culture-proven acute *Coccidioides* spp. infection in San Diego, California, United States. Mycoses 2020;63:553–7, doi:http://dx.doi.org/10.1111/myc.13074.
[35] Roberts PL, Knepshield JH, Wells RF. *Coccidioides* as an opportunist. Arch Intern Med 1968;121:568–70 PMID: 5652410.
[36] Blair JE, Balan V, Douglas DD, Hentz JG. Incidence and prevalence of coccidioidomycosis in patients with end-stage liver disease. Liver Transpl 2003;9:843–50, doi:http://dx.doi.org/10.1053/jlts.2003.50125.
[37] Ampel NM, Mosley DG, England B, Vertz PD, Komatsu K, Hajjeh RA. Coccidioidomycosis in Arizona: increase in incidence from 1990 to 1995. Clin Infect Dis 1998;27:1528–30, doi:http://dx.doi.org/10.1086/515044.
[38] Weatherhead JE, Barrows BD, Stager CE, Finch CJ, El Sahly HM. Gastrointestinal coccidioidomycosis. J Clin Gastroenterol 2015;49:628–9, doi:http://dx.doi.org/10.1097/MCG.0000000000000326.