Coccidioidomycosis in times of Covid-19: review and analysis of reported cases

Coccidioidomicosis en tiempos del Covid-19: Revisión y análisis de casos reportados

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ABSTRACT

Introduction: Coccidioidomycosis (CM) is a systemic, underdiagnosed disease caused by the soil fungi *Coccidioides immitis* and *C. posadasii*. It is endemic to desertic regions of the Americas. With the recent pandemic emergency for SARS-CoV-2, all eyes were on Covid-19 in healthcare institutions. Covid-19 is a respiratory disease with symptoms resembling pulmonary CM. However, some pulmonary CM cases are prone to be missed due to the difficulties in diagnosing CM and its overlapping symptoms with Covid-19.

Objetive: To identify the delay in CM diagnosis due to Covid-19 suspicion and possible risk factors associated with disease severity.

Materials and method: This study is a case-series review and analysis of CM patients during the Covid-19 pandemic. A systematic search for possible coinfection cases with Covid-19 and CM was performed using the Google Scholar algorithm. The words "Covid-19", "Coccidioidomycosis," "SARS-CoV-2", "Coccidioides," "Case Report," and "Coinfection" were used with a range of time between 2019 and 2021.

Results: Nine case reports were obtained with selection criteria (n=9), the median age was 50 years old, 77.7% male patients, mainly Hispanic (66.6%), and most of them with comorbidities. 44.4% of cases had delayed CM diagnosis in more than four weeks, 33.3% died, and were receiving corticosteroids.

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RESUMEN

Introducción: La coccidioidomicosis (CM) es una enfermedad subdiagnosticada causada por *Coccidioides immitis* y *Coccidioides posadasii*. Es endémica de regiones desérticas de América. Durante la reciente pandemia de SARS-CoV-2, toda la atención se centró en el Covid-19; una enfermedad respiratoria con síntomas pulmonares similares a la CM pulmonar. Sin embargo, algunos casos de CM pudieron haber sido propensos a perderse debido a las dificultades en su diagnóstico y similitud de síntomas con Covid-19.

Objetivo: Identificar el retraso en el diagnóstico de CM debido a la sospecha de Covid-19 y posibles factores de riesgo asociados con mayor severidad de la enfermedad.

Materiales y método: Este es un análisis de serie de casos de CM durante la pandemia de Covid-19. Se realizó una búsqueda sistemática de posibles coinfecciones con Covid-19 y CM utilizando el algoritmo de Google Scholar. Se usaron las palabras “Covid-19”, “Coccidioidomycosis”, “SARS-CoV-2”, “Coccidioides”, “Case Report”, y “Coinfection” con un intervalo de 2019 – 2021.

Resultados: Se identificaron nueve casos que alcanzaron los criterios de selección (n = 9), la mediana de edad fue 50 años, 77.7% masculinos, la mayoría Hispanos (66.6%), y con comorbilidades. 44.4% de los casos tuvieron retraso en el diagnóstico de más de cuatro semanas, 33.3% murieron, y estaban recibiendo corticosteroides.

INTRODUCTION

Coccidioidomycosis or Valley fever is a systemic disease caused by a soil fungus. It starts with lower pulmonary involvement, and asymptomatic infections can reach up to 60% of all cases. While most cases resolute spontaneously, ~1% of patients can develop disease dissemination to other tissues, including muscles, bones, joints, skin, and central nervous system, where the last one has the worst prognostic [1]. It is an endemic disease restricted to desertic regions of the Americas in which the zone with major endemicity is along with the US-México border territories. The causal agents of this disease are biphasic soilborne fungi named *Coccidioides immitis* and *C. posadasii*, which display no morphological, serological, and clinical differences [2] as far as is known. Some risk factors for acquiring coccidioidomycosis (CM) are occupational and

habits involving soil contact. In comparison, risk factors for disease dissemination are immunosuppression and genetic background.

Moreover, there are no clinical or radiological findings suggesting unequivocally a Valley Fever diagnosis, by which laboratory tests are the cornerstone to achieve it [3]. Therefore, it seems that for every four ongoing CM cases, three will not be diagnosed in the United States [4]; therefore, it can be considered an underdiagnosed disease. Nonetheless, with the recent global pandemic emergency for SARS-CoV-2, all eyes are currently on Covid-19 in healthcare institutions. Covid-19 is a respiratory syndrome disease with similar symptoms resembling pulmonary CM. However, the difficulties in diagnosing coccidioidomycosis and its overlapping symptoms spectra with Covid-19, some pulmonary CM cases are prone to be missed. Thus, causing a delay in coccidioidomycosis diagnosis and treatment with antimycotic administration [5]. On the other hand, some coinfection cases have been recently documented [6–12], and others have shown significant delay because of cognitive bias [13,14]. Therefore, coinfection is crucial to detect because the outcomes of both diseases depend on comorbidities and opportune diagnosis.

The objective is to identify the delay in CM diagnosis due to Covid-19 suspicion and possible risk factors associated with patients for disease severity.

MATERIALS AND METHOD

This study is a reported cases review and analysis of CM patients during the Covid-19 pandemic. A systematic search for possible coinfections cases with Covid-19 and CM was performed using the Google Scholar algorithm in November 2021. The words "Covid-19", "Coccidioidomycosis," "SARS-CoV-2", "Coccidioides," "Case Report," and "Coinfection" were set in different combinations in the search bar, while the range of time was between 2019–2021. Up to 195 results were found and systematically reviewed to select only case reports articles in scientific journals published since 2019. First, those cases where coccidioidomycosis diagnosis was clinically established, including at least one laboratory test positive, were selected. A second aspect was SARS-CoV-2 infection, first considered cognitive bias caused by the pandemic emergency. SARS-CoV-2 was assessed by checking first diagnosis suspicion and at

least one real-time PCR swab test (or equivalent) for SARS-CoV-2 detection done. Finally, PubMed indexation of the journal was the third requisite criterion for inclusion of case reports articles; 8 of 9 published case reports are published in Web of Science indexed journals. Unfortunately, this study did not include online published abstracts of case reports because of missing data.

RESULTS

A condensation of the most essential data for these reported cases is included in Table 1. Nine case reports were found to meet the selection criteria (n = 9), the median age was 50 years old (23 – 67), 77.7% were male patients, mainly Hispanic people (66.6%), and most of them had known comorbidities. At least 44.4% of case reports had delayed CM diagnosis in more than four weeks since the first presentation to a health care practitioner's attention [7,8,10,14]. Covid-19 was the first suspected disease in all of them, and one case received treatment for such disease, despite negative results for the SARS-CoV-2 test. While for diagnosing CM, serology was used, followed by histology of tissue biopsy. In one case, serology showed negative results, resulting in a delay of ~six months for final diagnosis [10]. A great variety of laboratory tests exist for diagnostic purposes, but some of them are not affordable in low-resource settings [3], making CM diagnosis far from being opportune.

TABLE I.

Case	I* [12]	II* [6]	III* [10]	IV* [11]	V* [7]	VI* [9]	VII* [8]	VIII‡ [14]	IX‡ [13]
Age (years old)	48	48	67	52	65	50	23	34	61
Sex	Male	Female	Female	Male	Male	Male	Male	Male	Male
Ethnic group	Hispanic	Hispanic	ND	Hispanic	Hispanic	Hispanic	African American	ND	Hispanic
Comorbi-dities	Uncontro-lled DM	Systolic heart failure	Asthma and asbestosis; Liposarcoma	Uncontrolled DM; Class I Obesity	Insulin-dependent DM	Smoking history and T2DM	ND	ND	HIV (VL = 309,000; CD4+ = 38)
Place of residence	CA (USA)	CA (USA)	TX (USA)	TX (USA)	CA (USA)	TX (USA)	ND	ND	TX (USA)
Hospitali-zation	No	Yes	ND	Yes	Yes	Yes	Yes	No	Yes
Days after onset for Covid19 diagnosis	8	1	ND	4	33 (PD)	0 (PD)	0	-	-
PCR or equivalent for SARS-CoV-2?	Yes (+)	Yes (+)	Yes (+)	Yes (+)	Yes (-)	Yes (+)	Yes (+)	Yes (-)	Yes (-)
Symptoms at first presenta-tion	Fever, cough and body aches	Dyspnea	Dyspnea, fatigue and cough	Dyspnea, cough, loss of appetite and fever,	Hypoxia	Dyspnea and cough	Mild febrile illness	Chest pain, fatigue, myalgia, intermittent fever and anorexia	Abdominal pain, loss of weight, weakness, general malaise, productive cough, nausea and diarrhea
Symptoms during evolution	Weakness progressive cough, fever and body aches,	Headache, cough, dyspnea, fever (38.2°C)	Improvement of respiratory symptoms, appearing of disseminated lesions	Worsening fever (40.5°C), hypoxia and respiratory failure	Progressive dyspnea, hypertension, tachypnea, and altered mental status	ND	Night sweats, loss of weight, ostealgia, non-painful ulcers and lymphadenopathy	Night sweats, fever (38.4°C) and mild non-productive cough	Respiratory failure, renal failure and septic shock
SaO_2 (%)	99 (RA)	93 (NC)	ND	ND (EI required)	70 (1A); EI required (3A).	88 (RA)	ND	94 (RA)	92 (RA)
First Treatment (or for Covid-19)	AZM	AZM, CTX and DEX (6 mg IV); RDV 200 mg IV on first day, followed by 100 mg/day; convalescent plasma.	ND	DEX 10 – 20 mg /24hrs doses for 20 days IV; RDV 200 mg on day 1, then 100 mg/day; convalescent plasma (1 unit); CFPM and VAN (UD)	DEX 6 mg (> 9 days use); ND AB	AZM, Vitamins C and D, and Zinc (UD)	None	Ibuprofen and Acetaminophen; AZM 500 mg/12 hrs for 5 days; CPDX 200 mg/12 hrs	CPFX and MTZ; CFPM and VAN (UD); IV Methylprednisolone 60 mg/8 hrs
Treatment after CM diagnosis/suspected	Yes, but not specified	FCZ 400 mg	FCZ 400 mg	-	L-AMB IV	L-AMB at first, then FCZ 600 mg/day PO	L-AMB 5 mg/kg IV (14 days); ICZ 200 mg/12hrs PO	ND	-
Delay in CM diagnosis (~ days)	0 (PD)	4	180	21	78	ND	33	47	3
Type of CM	Pulmonary	Pulmonary	Disseminated	Pulmonary	Disseminated	Pulmonary	Disseminated	Pulmonary	Disseminated CM
Laboratory tests for *Coccidioides* spp.	CF (1:32) in serum	EIA IgM (+) in serum	IgM/IgG (-) EIA; Histology of chest wall	Fungal culture of BAL and MALDI-ToF	Histology of skin biopsy	*Coccidioides* antigen (EIA) in serum	Histology of lymph node and skin biopsy	EIA IgM (+) IgG (-) in serum	Histology of lymph node and skin biopsy
Death	No	No	No	Yes	Yes	No	No	No	Yes

AB = Antibiotics; AZM = Azithromycin; BAL = Bronchoalveolar lavage; CF = Complement fixation; CTX = Ceftriaxone; CFPM = Cefepime; CPDX = Cefpodoxime; CPFX = Ciprofloxacin; D = Day after hospitalization; DEX = Dexamethasone; DM = Diabetes mellitus; EI = Endotracheal intubation; EIA = Enzyme immunoassay; FCZ = Fluconazole; IV = Intravenous L-AMB = Liposomal amphotericin B; MALDI-ToF = Matrix-assisted laser desorption/ionization time-of-flight; MTZ = Metronidazole; NC = Nasal cannula; ND = Not declared; PD = Previously diagnosed; PO = Orally; RA = Room air; SaO_2 = Oxygen saturation; VAN = Vancomycin; T2 = Type 2; UD = Unspecified dose; 1A = First admission; 3A = Third admission; *= Presumptive coinfection; ‡= Suspected Covid-19 at first but CM; ~ = Approximate

DISCUSSION

It is vital to notice that two of these cases had a fatal outcome [7,11], despite hospitalization; also, it can be observed that they were receiving long-term treatment with corticosteroids. One more fatal case received methylprednisolone, but it was an HIV patient with a low count of CD4+ cells [13], which is a well-known risk factor for active CM [15] and possibly for reactivation [16]. The use of corticosteroids has been previously related to disseminated CM [17], which probably contributed to these patients' lack of response. On the contrary, beneficial results have been observed when short-term corticosteroids are co-indicated with antifungal therapy on meningeal CM [18]. This practice may be reflected in the case presented by Chang et al. [6], who considered such risk factors as a determinant for co-administration with Fluconazole (FCZ). However, only three of each 9 case reports considered corticosteroids in work discussion [7,9,11]. Severe Covid-19 treatment protocols consider using corticosteroids as first-line therapy to deal with cytokine storm [19]. Meanwhile, the use of this therapy alone is not appropriate in CM. Physicians in CM endemic regions should be aware of this possibility to avoid possible complications.

The diagnosis of coccidioidomycosis in endemic areas is a challenge for health care providers because of the likelihood of clinical presentation of infectious diseases. It becomes even more defiant in the season of co-circulation of pathogens like Influenza, Syncytial Respiratory Virus, and more recently, SARS-CoV-2. Even though almost half of the cases here reviewed had a diagnosis delay of more than 30 days, this result is not different than those in larger cohorts. Ginn et al. [20] observed similar findings, with 46% of CM diagnoses among the second and sixth months since first presentation.

CONCLUSION

This study has an evident weakness because of the reduced number of cases, while no more were available in literature. To confirm these observations, surveillance in CM should continue while the SARS-CoV-2 threat is still present.

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Conflicts of Interest. The authors declare no conflict of interest.

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