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Disseminated coccidioidomycosis with giant coccidioidoma of the suprarenal gland. Autopsy case report

Coccidioidomicosis diseminada con coccidioidoma gigante de la glándula suprarrenal. Reporte de caso de autopsia

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Keywords: Coccidioidomycosis, coccidioides immitis, coccidioides posadasii, coccidioidoma.

Palabras clave: *Coccidioidomicosis, coccidioides immitis, coccidioides posadasii, coccidioidoma.*

ABSTRACT

Coccidioidomycosis is an endemic systemic mycosis produced by *Coccidioides*. The fungus is endemic to arid zones of North America. Two species with infectious potential are known: *Coccidioides immitis*, responsible for infections in the states of California, Texas, Arizona, and New Mexico (USA) and *Coccidioides posadasii*, endemic to the deserts of northern Mexico. We present a case of disseminated coccidioidomycosis, with a coccidioidoma of the left suprarenal gland studied at Hospital General de México «Dr. Eduardo Liceaga». In cases of primary hematogenous dissemination, it is more common for the course of the disease to have a fatal outcome; such cases are associated with factors of immunocompromise. In conclusion, coccidioidomycosis is very uncommon in its disseminated form. The formation of fungal balls is not exclusive to the lungs, since it can be found in any infected organ, even in the suprarenal gland.

RESUMEN

La coccidioidomicosis es una micosis sistémica endémica producida por los coccidioides. *El hongo es endémico de las zonas áridas de América del Norte. Se conocen dos especies con potencial infeccioso:* Coccidioides immitis, *responsable de las infecciones en los estados de California, Texas, Arizona y Nuevo México (EE.UU.) y* Coccidioides posadasii, *endémica de los desiertos del norte de México. Presentamos un caso de coccidioidomicosis diseminada, con un coccidioidoma de la glándula suprarrenal izquierda estudiado en el Hospital General de México «Dr. Eduardo Liceaga». En los casos de diseminación hematógena primaria, es más común que el curso de la enfermedad tenga un resultado fatal; tales casos están asociados con factores de compromiso inmunológico. En conclusión, la coccidioidomicosis es muy poco común en su forma diseminada. La formación de bolas fúngicas no es exclusiva de los pulmones, ya que se encuentra en cualquier órgano infectado, incluso en la glándula suprarrenal.*

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INTRODUCTION

Coccidioidomycosis is an endemic systemic mycosis produced by dimorphous fungi of the genus *Coccidioides*, which infect humans and other species through inhalation in the form of arthroconidia. The fungus is endemic to arid zones of North America.[1,2] Two species with infectious potential are known: *Coccidioides immitis*, responsible for infections in the states of California, Texas, Arizona, and New Mexico (USA) and *Coccidioides posadasii*, endemic to the deserts of northern Mexico.[3] Sixty percent of *Coccidioides* infections are asymptomatic and indistinguishable from an upper respiratory tract infection; the other 39% develop a symptomatic pulmonary primoinfection and only 1% present disseminated extrapulmonary

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infection, primarily affecting the central nervous system, skin, bones, and joints.[4,5] In its saprophytic phase, the fungus is inhaled in the form of arthroconidia which, when they infect the host, form spherules with endospores, which are released. It is possible to identify different parasitic forms which include hyphae, arthroconidia, and coccidioidomas, although the latter are very rare.[4] We present a case of disseminated coccidioidomycosis, with a coccidioidoma of the left suprarenal gland studied at Hospital General de México «Dr. Eduardo Liceaga».

CLINICAL SUMMARY

Background: Diabetes mellitus of two months' evolution, with irregular treatment. Smoking of 20 years' evolution at a rate of six cigarettes a day. Fall from his own height in June 2016 without needing hospitalization.

Final condition: Onset three months prior to hospitalization, with sudden deterioration of alert state, ataxia, dyslalia, speech impediment and holocranial headache which did not cede with analgesics. A week before admission, patient presented loss of bowel control and visual hallucinations, for which he went to a hospital, where he was admitted for six days with evaluation by the Psychiatric Service, who diagnosed him with psychotic break and prescribed haloperidol and risperidone without improvement. A second evaluation was sought from a private physician, who suspected probable infectious or metabolic etiology and requested cranial tomography, in which no alterations were observed. Under these conditions, the patient was admitted to Hospital General de México «Dr. Eduardo Liceaga».

Physical exploration at admission

Vital signs: blood pressure 100/70 mmHg, heart rate 98 bpm, respiratory rate 40 rpm. Male patient 69 years of age, cachectic, with pallidity of skin and teguments, without central cyanosis, nostrils permeable, oral mucosa dehydrated, anisocoria with left mydriasis; pupillary, consensual, and photomotor reflex preserved. Precordial area with rhythmic cardiac sounds of adequate intensity, without aggregates. Thorax with bilateral lung crackles, predominantly left in the interscapular vertebral region, without sibilance. Abdomen flat, depressible, without signs of peritoneal irritation, no palpable organ enlargement or tumors. Glasgow 14, disoriented in time, place, and person, with incomprehensible speech.

Evolution and treatment

Patient was admitted to the emergency ward with clinical diagnosis of probable neuroinfection. During his stay in the service, a chest X-ray was taken, which showed the presence of multiple disseminated micronodular lesions, based on which miliary tuberculosis was suspected. He was referred to the Pneumology Service, where he experienced deterioration of respiratory function for which advanced airway management was instituted. He was transferred to Pneumological Intensive Care, where he presented with signs of adult respiratory distress syndrome and a new cranial tomography was taken, which reported no abnormal findings. Lumbar puncture was performed for mycobacterial culture, direct examination of fungi, fungal cultures, cytological and cytochemical

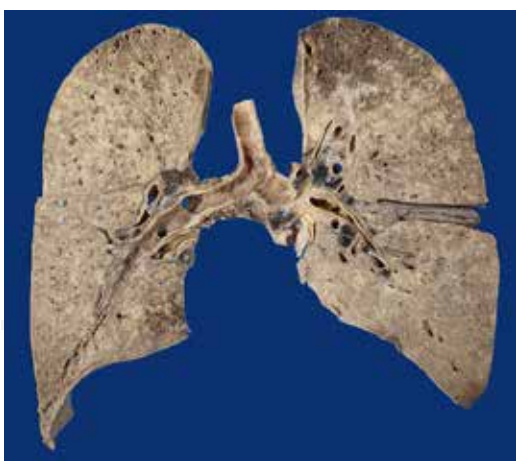

Figure 1. Lungs with nodules irregularly distributed in all lobes.

Figure 2. Left lung with bronchiectasis predominantly in the upper lobe.

Figure 3. Left lung with a cavern in the lower lobe.

studies, which diagnosed probable mycobacterial etiology. Treatment was instituted with DOTBAL and antifungal treatment with amphotericin B. Patient presented with drop in blood pressure, absence of respiratory sounds with right tension pneumothorax, for which an emergency endopleural catheter was placed; however, he presented irreversible cardiorespiratory arrest.

Laboratory and examining room tests

Blood chemistry: 18.10.16: glucose 196 mg/dL, urea 39 mg/dL, creatinine 0.8 mg/dL, uric acid 1.6 mg/dL.
Blood biometry: 18.10.16: leukocytes 3.5 x 10e3/uL,

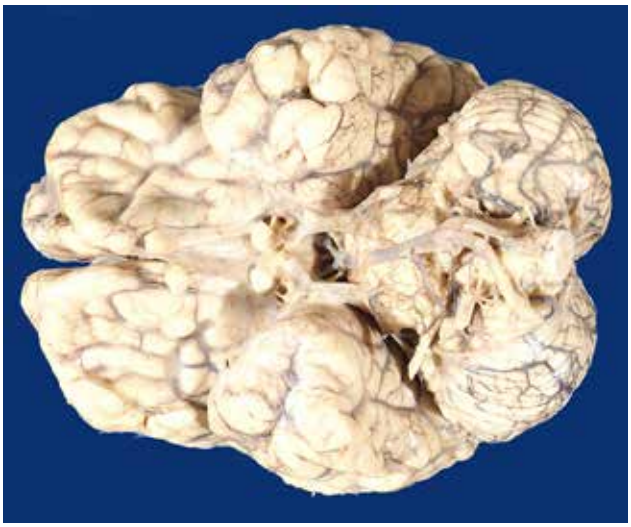

Figure 4. Ventral surface of the brain with thickening of the leptomeninges.

Figure 5. Brain stem with leptomeningeal thickening that compresses nerves.

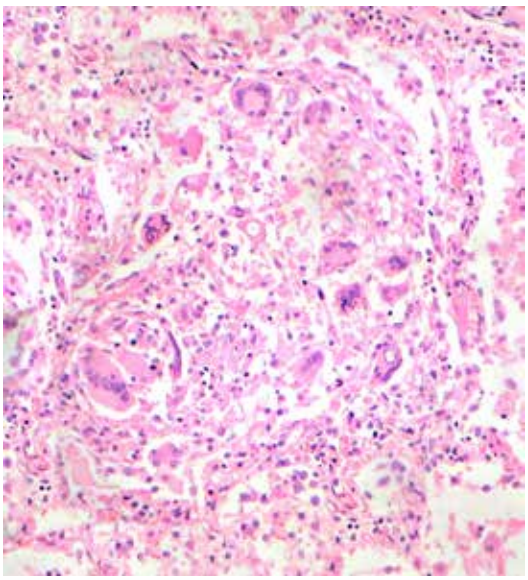

Figure 6. Lung with granulomas with multinucleated giant cells that have phagocytosed microorganisms.

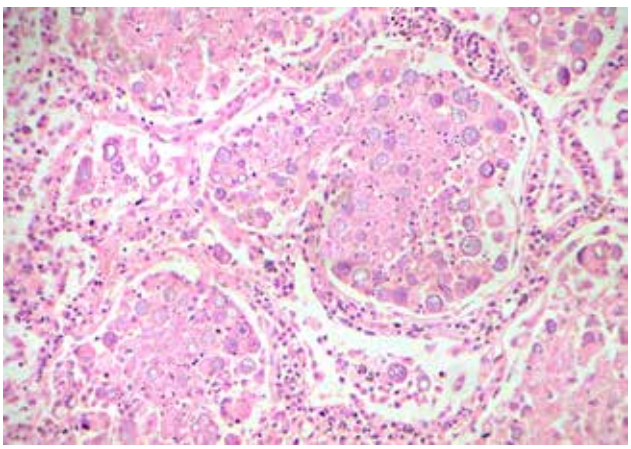

Figure 7. Lung with air spaces occupied by numerous spherules with endospores of *Coccidioides spp*.

neutrophils 83%, hemoglobin 11.7 g/dL, hematocrit 24.4%, platelets 180 x 10e3/uL.

Final clinical diagnose

Septic shock with pulmonary focus.
Probable disseminated tuberculosis.
Probable disseminated coccidioidomycosis.
Severe ARDS.
Right tension pneumothorax.

Summary of autopsy

The autopsy found increased weight of the lungs. On the pleural surface, multiple light gray nodules were observed, measuring 0.5 x 0.5 x 0.1 cm with well-defined limits, distributed irregularly in both lungs; in slices, similar lesions were observed with casseous appearance distributed throughout the pulmonary parenchyma *(Figure 1)*. In the upper lobe of the right lung, bronchiectasis and bronchiolectasias were found *(Figure 2)* and the lower left lobe presented a pitted

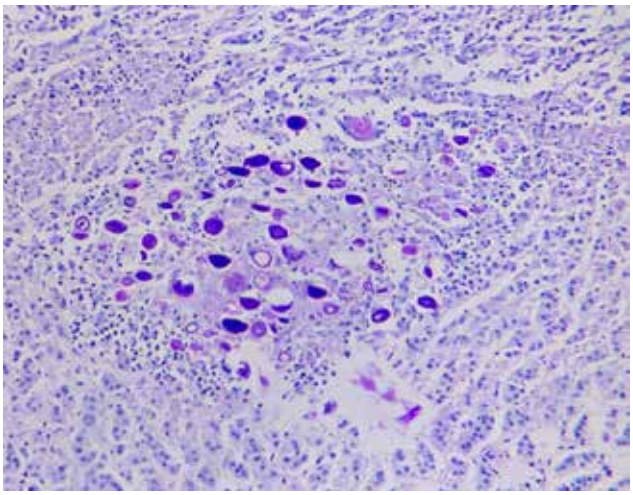

Figure 8. Liver with granulomas among which numerous spherules are identified.

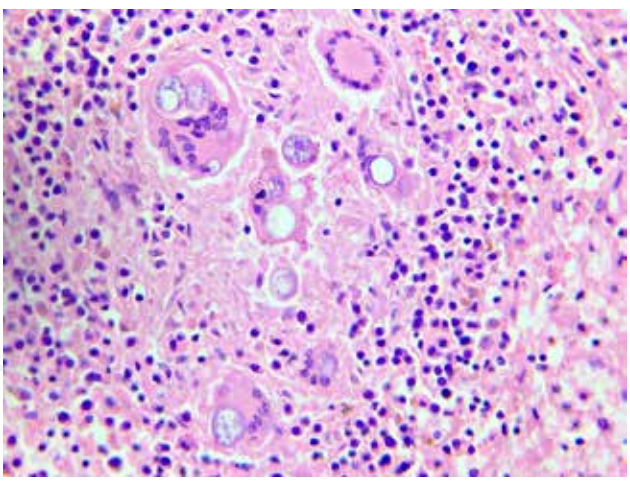

Figure 9. Spleen with granulomas with Langhans giant cells and foreign body reaction associated with spherules with endospores.

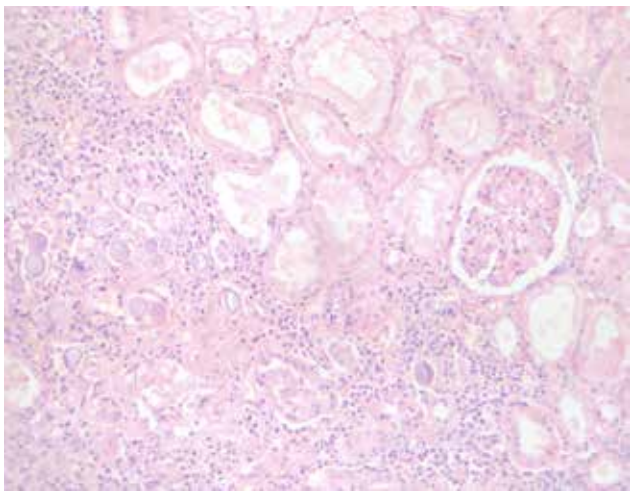

Figure 10. Kidney with numerous microorganisms in the interstitium.

Figure 11. Left adrenal coccidioidoma.

area measuring 4.2 x 3.5 x 3.3 cm, with subpleural localization and heterogeneous inner surface with hemorrhagic areas alternating with areas of casseous appearance *(Figure 3)*.

In the encephalon, the arachnoidea was opaque, grayish white in color, with bilateral frontoparietal predominance and leptomeningeal thickening of the ventral surface *(Figures 4 and 5)*, surrounding and compressing the cranial nerves and circle of Willis.

The microscopic study observed, in the lungs *(Figures 6 and 7)*, thoracic lymph nodes, liver *(Figure 8)*, spleen *(Figure 9)*, thyroid gland, kidneys *(Figure 10)*, and leptomeninges, the architecture altered by numerous granulomas with multinucleated foreign body and Langhans giant cells in response to the presence of numerous spherules measuring 20 µm in diameter on average, with double basophil layer, within some of which endospores corresponding to fungal microorganisms of the genus *Coccidioides spp*. are preserved in their pathogenic levaduriform phase, even observing the phenomenon of endospore expulsion.

The left suprarenal gland was prominent, presenting a nodular lesion, with expansive edges, measuring 4 x 3 x 3 cm, light gray in color, with hard consistency, which was provisionally diagnosed as an «atypical» adenoma *(Figure 11)*; however, histologically it was made up by granulomas, casseous necrosis, and multiple spherules with endospores positive to periodic acid-Schiff *(Figures 12 and 13)* and Grocott staining *(Figure 14)* similar to those described in other organs.

With these data, we diagnosed systemic coccidioidomycosis affecting lungs, lymph nodes, liver, spleen, thyroid gland, kidneys, and leptomeninges with left suprarenal coccidioidoma.

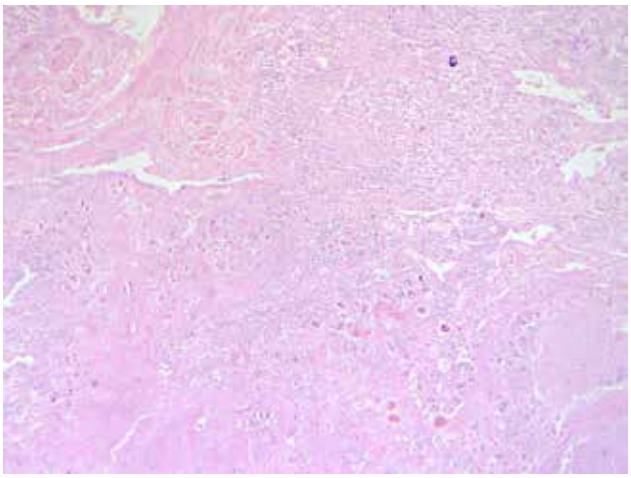

Figure 12. Adrenal gland with extensive areas of caseous necrosis and numerous microorganisms.

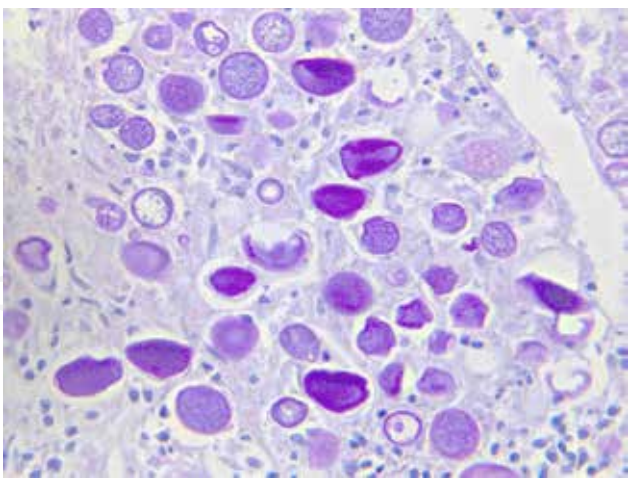

Figure 13. Empty spherules and others with endospores.

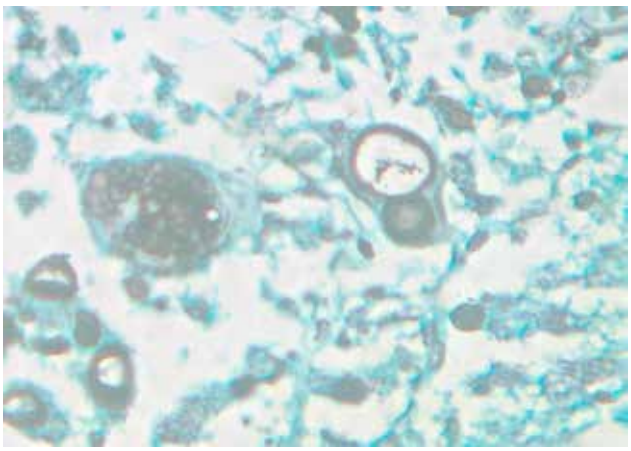

Figure 14. Spherule releasing endospores.

DISCUSSION

One third of coccidioidomycosis infections are symptomatic, mostly presenting as pneumonia. In cases of primary hematogenous dissemination instead of classic pulmonary infection, it is more common for the course of the disease to have a fatal outcome; such cases are associated with factors of immunocompromise such as: human immunodeficiency virus infection (low CD4 T lymphocyte count < 200 u/L), systemic corticosteroid therapy, lymphoid neoplasms, autoimmune disease, pregnancy, and diabetes.[5,6]

As regards predisposition based on ethnicity, a higher incidence has been documented in black and Philippine males; it is uncommon in Latinos, unless they have a risk factor, which in most cases is diabetes mellitus. Diagnosis is often delayed because serological tests in severely immunocompromised patients are usually negative; studies commonly used to confirm diagnosis are culture and histopathology after bronchoscopy.[6]

Histopathologically, three weeks after infection an inflammatory response begins based on classic granulomas with epithelioid cells, casseous necrosis, and lymphoplasmacytic infiltrate, accompanied by spherules with endospores in their interior. When the infection is chronic, the granulomas are surrounded by collagen fibers.[1] In our case, blood sugar levels remained high and the patient was unaware he was diabetic until two months before his death. Due to such immunosuppression, the clinical form of presentation included neurological symptoms due to arachnoidal dissemination and miliary lung disease, which are manifestations with poor prognosis.

The anatomopathological forms of presentation of coccidioidomycosis are varied and are divided in typical (spherules) and atypical (mycelia); however, the latter have been seen more often in chronic lung disease of 8 months' to 2.5 years' evolution and with comorbidities like type 2 diabetes mellitus, which favor the growth of all the parasitic forms of the fungus. From both a clinical and histopathological standpoint, several forms of presentation of *Coccidioides sp*. have been found: a) spherules/endospores in varying degrees of maturation, b) septate hyphae and pleomorphic cells, c) arthroconidia (rectangular, ovoid, or barrel-shaped) and d) balls of fungi (coccidioidomas).[7] In this case, histopathologically, two of the forms described were found: spherules with endospores and a suprarenal coccidioidoma.

From a radiographic standpoint, pulmonary coccidioidomycosis has different categories: 1) bronchopneumonia, acute and persistent with chronic fibrocavitary disease, 2) cavities, 3) hilar adenopathy, 4) nodules (coccidioidoma), which are usually associated with cavitations.[8] In this case we found fibrocavitary disease, miliary disease, and hilar adenopathy.

Visceral compromise by this fungus is rare, the organs involved are commonly those of the genital tract, liver, spleen, peritoneum, and even the heart.[1,5] The suprarenal gland is a site rarely affected by mycotic diseases; however, some cases have been described where they are accompanied by disseminated mycoses. Such cases involve to other fungi like *Paracoccidioides sp.*, which has a high affinity for the suprarenal gland, with an incidence of 85-90% in autopsy studies, *Histoplasma sp*. (a published case), *Blastomyces sp.*, and *Cryptococcus sp.*,[9,10] which have even formed lesions so large that their primary differential diagnosis is neoplastic, as occurred in this case.

In conclusion, coccidioidomycosis is very uncommon in its disseminated form. The formation of fungal balls or coccidioidomas is not exclusive to the lungs, since it can be found in any infected organ, even in the suprarenal gland, which has very scant affinity for the fungus.

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