

COCCIDIOIDOMYCOSIS IN BRAZIL. A CASE REPORT

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SUMMARY

Coccidioidomycosis is an endemic infection with a relatively limited geographic distribution: Mexico, Guatemala, Honduras, Colombia, Venezuela, Bolivia, Paraguay, Argentina and the southwest of the United States. In these countries, the endemic area is restricted to the semiarid desert like regions which are similar to the northeast of Brazil. Case report: The patient is a 32 year-old male, born in the state of Bahia (Northeast of Brazil) and has been living in São Paulo (Southeast) for 6 years. He was admitted at Hospital das Clínicas, at the Department of Pneumology in October 1996, with a 6 month history of progressive and productive cough, fever, malaise, chills, loss of weight, weakness and arthralgia in the small joints.

Chest x-rays and computerized tomography disclosed an interstitial reticulonodular infiltrate with a cavity in the right upper lobe.

The standard potassium hydroxide preparation of sputum and broncoalveolar lavage demonstrated the characteristic thickened wall spherules in various stages of development. Sabouraud dextrose agar, at 25° C and 30° C showed growth of white and cottony aerial micelium. The microscopic morphology disclosed branched hyphae characterized by thick walled, barrel shaped arthroconidia alternated with empty cells.

The sorological studies with positive double immunodiffusion test, and also positive complement fixation test in 1/128 dilution confirmed the diagnosis. The patient has been treated with ketoconazole and presents a favorable clinical and radiological evolution.

KEYWORDS: Coccidioidomycosis; Pulmonary mycosis.

INTRODUCTION

Coccidioidomycosis is an infection caused by a geophilic fungus, *Coccidioides immitis* RIXFORD & GILCHRIST, 1896²⁰ diagnosed for the first time in Argentina by POSADAS (1892)¹⁹ and WERNICKE (1892)²³ in isolated works, with an initial diagnosis of mycosis fungoides with psorosperm.

In 1894 and 1896, in California, the first cases of the infection were registered, followed by the isolation of the fungus from the soil of desert-like areas in the so-called San Joaquin Valley. Soon, the concepts of coccidioidomycosis infection detected through coccidioidin skin test, were established. After that, this antigen was also used under another form, called spherulin, since in the latter process, the antigen was standardized with the parasitary form of the fungus (spherules obtained *in vitro*).

It is the predominant infection in San Joaquin Valley, in California. Other endemic areas were detected later, through the use of the coccidioidin skin test, in Colombia, Venezuela, Mexico, Guatemala, Honduras, El Salvador, Bolivia, Paraguay and Argentina. According to WANKE (1994)²² the areas which offer the greatest risk are holes of small animals such as rodents and marsupials and archeological sites, specially cemeteries. In these areas, where the soil is usually alkaline and presents elevated salinity, the fungi proliferate in the filamentous form, yielding very characteristic arthroconidia.

The fungi in its arthroconidia form with disjunctors is found in the soil and the infecting particles penetrate the respiratory system of man and animals (usually rodents) through inhalation, causing asymptomatic infections or progressive diseases with

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pulmonary, skin, osteo-articular and meningo-encephalic lesions, specially. There is no doubt that coccidioidomycosis is a regional pathology, where the bioclimatic conditions of the environment promote the development of the fungi in dry and arid soil with xerophilic vegetation and low rainfall. Arthroconidia disseminate through air currents, becoming spherules in the human or animal host. In Brazil there have been few cases of coccidioidomycosis reported to date. Attention was called to the problem by WANKE (1994)²² when he described the simultaneous infection in three patients, 2 adults and a 12-year-old boy, all of which took part in an armadillo hunt in the rural area of Oeiras, State of Piauí, Brazil.

Ten days after they had excavated the soil to remove the armadillo from its hole, the three patients and 8 dogs, also present at the hunt, showed symptoms of the infection, with fever and respiratory illness. The fungi was isolated from sputum samples of two of the patients and found in the lungs of one of the infected dogs. Complementary studies allowed the isolation of *Coccidioides immitis* in soil samples collected from the excavation site. Before Wanke's observations GOMES et al. (1978)⁸ registered a case of coccidioidomycosis in a patient from Paripiranga, State of Bahia, Brazil diagnosed in a surgical sample from the lower left pulmonary lobe of a patient who presented hemoptysis. The pulmonary radiological assessment disclosed heterogeneous opacity with cavity image corresponding to the apical segment of the lower left pulmonary lobe. This feature was confirmed through planigraphy and bronchography. The patient was submitted to a lobectomy (lower left lobe) and was released from the hospital 10 days after surgery. In the following year, VIANNA et al. (1979)²¹, in Brasília/DF, Brazil, described a new case in a male patient, who was a farmhand from the State of Piauí, Brazil. He had always lived in his home state and his pulmonary biopsy allowed the diagnosis of the infection. This patient's complaints was epigastralgy without any other symptoms, and good general state. Torax x-ray revealed multiple pulmonary nodules localized primarily on the base and middle fields, some of them calcified. Coccidioidin skin test was

positive. SIDRIN et al. (1997)¹⁵ registered 4 cases of coccidioidomycosis in the northeast of Brazil in farm workers from Aiuaba (southeastern part of state of Ceará) which is located in a semi-arid area, and nowadays considered to be an endemic area for this disease. All of them were armadillo hunters, animal used as food in the area. Pulmonary lesions were found in three patients. All of them presented fever and non-productive cough, simulating a cold. In 1997, SILVA et al.¹⁶ described with more accuracy the 4 cases registered by SIDRIN et al. (1997)¹⁵.

In 1996 KUHL et al.⁹ registered a case with a larynx polypoid lesion with a histopathological diagnosis of coccidioidomycosis. In the same year, MARTINS et al.¹³ published the case of a female patient in Rio de Janeiro with acute lymphoblastic leukemia and pulmonary lesions of progressive coccidioidomycosis with fatal evolution.

When Lutz (1908) examined the sample sent by Wernicke from Buenos Aires, he stated that he had never seen endogenous sporulation in his two cases of coccidioidomycosis. Roberto Wernicke was a Professor of Pathology in the School of Medicine in Buenos Aires and Alejandro Posadas was a surgeon. The comparative study between the coccidioidal and paracoccidioidal granulomas performed by ALMEIDA (1930)^{1,2,3} allowed this mycologist to establish the gender *Paracoccidioides*, also showing, in 1943, that *Paracoccidioides mazzai* Fonseca, 1928⁷, registered from a case with larynx lesions in Argentina, case that was observed by MAZZA & PARODI (1927)¹⁴ was identical to *C. immitis*. Still regarding coccidioidomycosis, LACAZ et al. 1978¹² obtained only one positive reaction in 357 individuals older than 11 years of age, in a research done with coccidioidin, using spherulin provided by Berkeley Biologic, California, U. S. A. This positive case was from the state of Bahia, and also presented positive reaction to paracoccidioidin and sporotrichin. In a patient with paracoccidioidomycosis the spherulin test was negative, confirming the work of VERSIANI (1946)¹⁷ who performed skin tests with coccidioidin in 28 patients with paracoccidioidomycosis.

TABLE 1

Cases of Coccidioidomycosis registered in Brazil.

1) GOMES et al. (1978) ⁸	Patient from the state of Bahia (Pirapiranga) with chronic progressive pulmonary process. Lower left lobectomy.
2) VIANNA et al. (1979) ²¹	Patient from the state of Piauí with multiple pulmonary nodules. Case studies in Brasília.
3) WANKE et al. (1994) ²²	Three patients, two adults and a 10 year old boy, observed in Oeiras, state of Piauí. Dogs also presented the infection.
4) KUHL et al. (1996) ⁹	Case registered in Ceará, (Crato region). Larynx lesion with polyp formation in the left vocal fold. Absence of pulmonary lesions.
5) MARTINS et al. (1997) ¹³	Female patient from Rio de Janeiro, with acute lymphoblastic leukemia and development of the pulmonary form of coccidioidomycosis, with progressed fast with fatal evolution.
6) SIDRIN et al. (1997) ¹⁵	Four cases of pulmonary coccidioidomycosis in armadillo hunters, observed in Aiuaba, state of Ceará. These cases were studied with more clinical details by SILVA et al. (1997).
7) MARTINS et al. (1997) (present data)	Patient with pulmonary coccidioidomycosis from the state of Bahia (Monte Santo, Drought Polygon). Patient was armadillo hunter. Favorable evolution with ketoconazole.

These data show the differences between coccidioidomycosis and paracoccidioidomycosis with their well defined and distinct etiological agents. In 1960 LACAZ et al.¹¹, among 750 adult individuals from different regions of Brazil, only one positive case was found, using coccidioidin diluted 1:100 (antigen provided by M. L. Furcolow). In his last work, LACAZ et al. remembered the possibility of spreading this research to other areas of Brazil, specially in the northeast, where the environmental conditions promote the saprophytic life of *C. immitis* in the soil.

In 1955, OLIVEIRA¹⁸ performed the test with coccidioidin diluted 1:100 and 1:1000, in 110 and 120 soldiers from the rural area of, respectively, the states of Santa Catarina and Paraná, southeastern part of Brazil, with negative results.

DIÓGENES et al.⁵, performing an epidemiological research with commercial spherulin in 87 individuals from Poço Comprido, Jaguaribe, Ceará, registered positive results in 26 and 11.5% of the samples, with 24 and 48-hours readings. The area where the study was performed is identified with the region of Oeiras, former capital of the state of Piauí, where Wanke registered coccidioidomycosis. In the state of Ceará, according to DIÓGENES et al. (1995)⁵ there was a case of larynx coccidioidomycosis, in a patient from Jaguaribara, which is a dry, semiarid region with scarce vegetation and abundant cactus, on the margins of Jaguaribe river.

In 500 patients habitants of Amazonia (Negro, Amazonas and Solimões rivers) the coccidioidin test has been negative (FONSECA et al, 1973⁶)

We believe, considering our data, WANKE'S (1994)²² and DIÓGENE'S (1995)⁵, that the states of Piauí and Ceará constitute areas of coccidioidomycosis due to their environmental conditions, differently from the southeast of our country. Further studies will be necessary to prove our assumption. With the register of observation in a patient from a place in Bahia, we can also consider part of this state as a reservoir of *C. immitis*.

Furthermore, there is no doubt we are facing a new problem of fungal pathology, specially in the northeast of our country. It is very difficult to evaluate if the geophilic fungus, the agent of the process, already existed in the northeastern soil or if it was brought through air currents from other endemic areas of coccidioidomycosis. Since the biological environment is at constant change, any statements made are just speculative.

CASE REPORT

I. S., thirty two years old, male, bricklayer, born in Monte Santo, State of Bahia, northeast of Brazil, has been living for eight years in São Paulo, State of São Paulo, southeast of Brazil, presented sporadic hemoptoic sputum, associated to weakness and turbid sight with worsening of the clinical picture. The frequency and intensity of those episodes increased insidiously, with concurrent myalgia, asymmetric arthralgia in small joints without phlogistic signs, loss of 8 kg,

fever and many episodes of infection of the upper respiratory tract. In 1996, six months after the worsening of such symptoms, he was attended at the Pneumology Service of the HCFMUSP, where a diagnostic investigation was initiated including several evaluations for tuberculosis (negative tuberculin reaction and negative sputum direct testing and culture). The patient also reported episodic headaches and light tiredness in case of habitual efforts, palpitations, inappetence, dyspepsia and intestinal constipation. The patient had a low social-economic level, lived in a primitive house, was a social etilist, ex-half pack a day smoker and used, since his childhood and during every revisit to his hometown, to hunt armadillos and eat the meat thereafter. He had never left his country and by the time he was attended he had not returned to his home state of Bahia for one year. On family history he revealed his grandfather died with a diagnosis of tuberculosis. On physical examination he was lucid, oriented, afebrile, hydrated, non-icteric, non-cyanotic and eupneic. Chest examination was compatible with the radiological finding. Chest x-rays showed interstitial reticulonodular infiltrate with a cavitary lesion in the right upper lobe (Fig. 1).

Computerized tomography showed interstitial reticulonodular infiltrate and a thick-walled cavitary lesion with irregularity of its surface in the posterior segment of the right upper lobe (Fig. 2). The standard potassium hydroxide preparation of sputum and broncoalveolar lavage demonstrated the characteristic thickened wall spherules in various stages of development (Fig. 3). In Sabouraud Dextrose Agar, at 25° C and 30° C showed growth of white and cottony aerial mycelium. The microscopic morphology exhibit branched hyphae characterized by thick-walled, barrel-shaped arthroconidia alternated with empty cells (Fig. 4). The serologic studies with positive double immunodiffusion test, and also positive complement fixation test in the 1/128 dilution confirmed the diagnosis (Fig. 5).

Complementary exams included negative anti-HIV serology.

DISCUSSION

The patient in this study is from Monte Santo, state of Bahia, located in the northeastern part of Brazil. The dry climate has maximum and minimum average temperatures of 35° C and 16° C, respectively.

The fauna is reduced to small animals and fowl. The patient was used to hunt armadillos, and so was exposed to the conidia of *C. immitis*.

He had been living in São Paulo for 6 years and had not returned to his home state since 1994. He started to present symptoms around 1991. He was admitted to the Service of Pneumology of Hospital das Clínicas in 1996, and chest x-rays and computed tomography disclosed an interstitial retinonodular infiltrate with a cavity in the right upper lobe.

The standard potassium hydroxide preparation of sputum and broncoalveolar lavage revealed the etiological

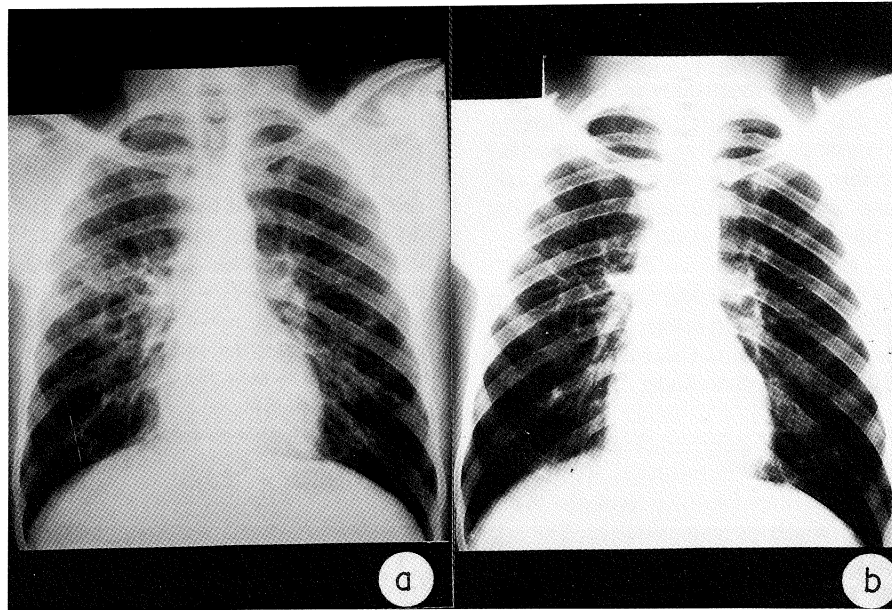


Fig. 1 – Chest radiographs: interstitial reticulonodular infiltrate with a cavitary lesion in the right upper lobe. a) pre-treatment; b) during treatment.

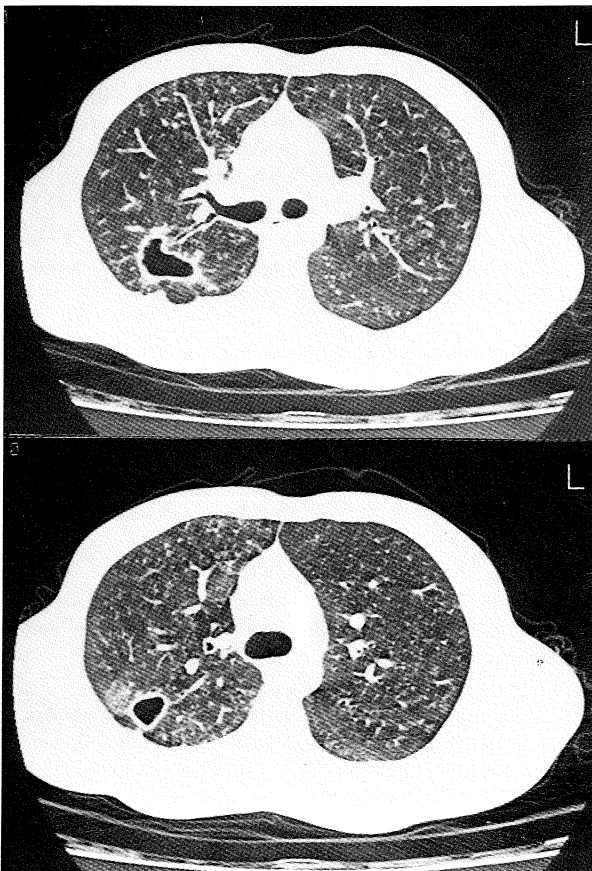


Fig. 2 – Computerized tomography: interstitial reticulonodular infiltrate and a thick-walled cavitary lesion with irregularity of its surface in the posterior segment of the right upper lobe.

agent, which was later cultivated. The serological studies with positive double immunodiffusion test, and also positive complement fixation test in 1/128 dilution confirmed the diagnosis. The patient has been treated with ketoconazole and presents a favorable clinical and radiological evolution.

We consider the northeast of Brazil as an endemic region for coccidioidomycosis. We conclude that patients with pulmonary manifestations similar to tuberculosis, from the northeastern region of our country, with negative acid-fast smears, must be evaluated for the possibility of coccidioidomycosis. We also point out that more extensive research must be carried out in this area in order to detect the coccidioidomycosis infection. We also stress the importance of isolating *C. immitis* from soil samples in that region. We also point out that the skin test with coccidioidin is negative in paracoccidioidomycosis (VERSIANI, 1946¹⁷ and LACAZ, 1948¹⁰)

RESUMO

Coccidioidomicose no Brasil. Registro de um caso

Coccidioidomicose é infecção endêmica com distribuição geográfica relativamente limitada: México, Guatemala, Honduras, Colômbia, Venezuela, Bolívia, Paraguai, Argentina e Sudeste dos Estados Unidos. Nestes países, a área endêmica está restrita a regiões desérticas ou semiáridas, semelhante as do Nordeste do Brasil.

Registro do caso: paciente masculino de 32 anos, nascido no Estado da Bahia (Nordeste do Estado), vivendo há seis anos em

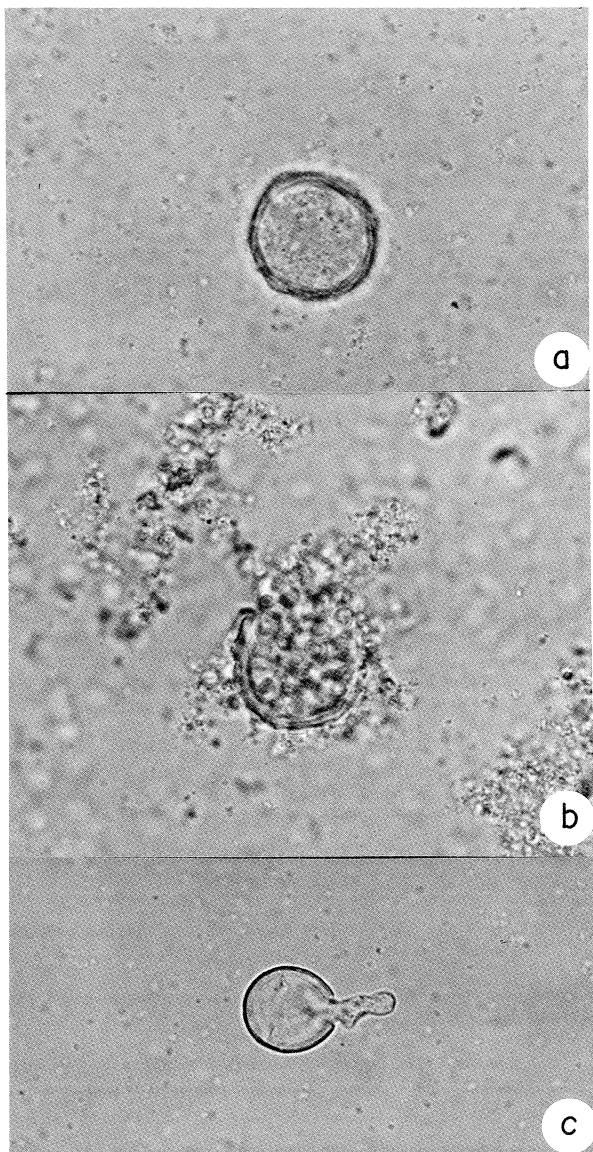


Fig. 3 – *Coccidioides immitis*. Direct microscopy of sputum, showing spherules in various stages of development ($\times 1000$).

São Paulo (Sudeste). Foi admitido no Departamento de Pneumologia do Hospital das Clínicas em outubro de 1996, com história de tosse produtiva e progressiva há seis meses, febre, mal estar, calafrios, perda de peso, fraqueza e artralgia das pequenas articulações.

Raio X e tomografia computadorizada revelou infiltrado retículo-nodular intersticial com cavidade no lóbulo superior direito. O exame direto do escarro e lavado broncoalveolar com hidróxido de potássio, demonstrou características esféricas de parede espessa em vários estágios de desenvolvimento. Sabouraud dextrose-ágar, à 25° C e 30° C permitiu crescimento de colônia branca, cotonosa.

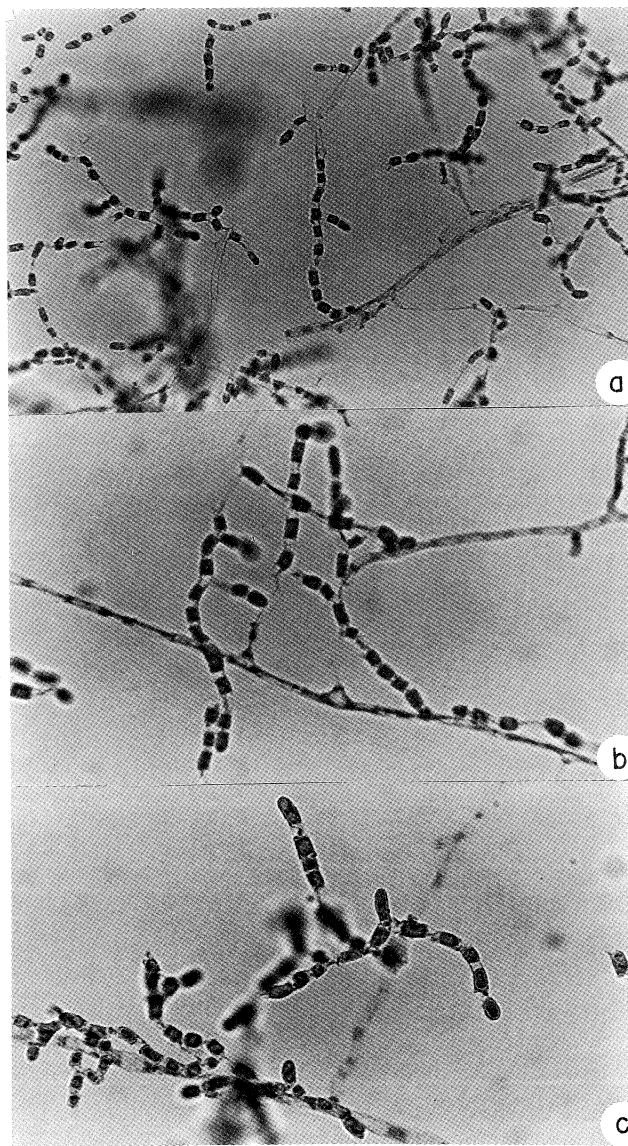


Fig. 4 – *Coccidioides immitis*. Microscopic morphology on potato dextrose agar: arthroconidia alternated with empty cells. a) $\times 630$; b, c) $\times 1000$.

A micromorfologia apresentou hifas ramificadas de parede espessa, arthroconídios em formas de barril alternadas com células vazias.

A prova de imunodifusão positiva e o teste de fixação de complemento positivo para 1:128 confirmaram o diagnóstico. O paciente está sendo tratado com ketoconazol e apresenta melhora clínica e radiológica.

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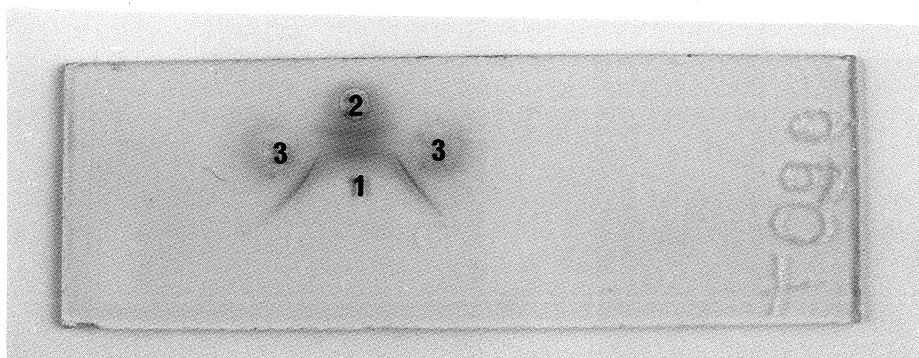


Fig. 5 – Double immunodiffusion test showing reactivity of the patient's serum with *Coccidioides* antigen.
1. *Coccidioides* antigen (IMMY, Inc., USA)
2. *Coccidioides* control serum (goat, IMMY, Inc., USA)
3. Serum from the patient with coccidioidomycosis

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