

## HISTOLOGICAL AND MICROBIOLOGICAL ASPECTS OF ACTINOMYCETOMA CASES IN VENEZUELA

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### S U M M A R Y

A ten year (1976-1986) review study of cases of Actinomycetoma in Venezuela was made through personal interview and clinical examinations, analysis of medical records of patients with actinomycetoma, histological studies of biopsy samples, as well as microbiological studies of isolates strain, also through out personal interviews with researchers and dermatologists who were sources of information on mycetoma cases. A total of 47 cases were recorded.

As etiologic agent *Actinomadura madurae* was found in 20 cases — (42.5%), *Nocardia brasiliensis* in 13 cases (27.6%), *Nocardia spp* 7 cases (14.8%), *Streptomyces somaliensis* in 4 cases (8.5%), *N. asteroides* in 2 cases (4.2%) and *N. otitidis caviarum*, (*N. caviae*) in 1 case (2.1%). Most of the reported cases involved individuals living and working in rural areas, mostly males who outnumber females 4:1. The patients were 18 to 80 years old. *A. madurae* was reported as the most frequent etiologic agent. Most of the clinical cases were seen when the disease was well established. Twenty four of the forty seven cases reported were observed in Lara State, which represents a 51.0% of all the cases studied.

**KEY WORDS:** Actinomycetoma — histopathology — incidence in Venezuela; Aerobic actinomycetales.

### I N T R O D U C T I O N

The term "Mycetoma" was used for the first time in 1860 by van Dyke Carter, to denote a fungus tumoral disease of the foot, later named "Madura foot" due to its prevalence in the province of Madura, India. 1 Mycetoma are caused by fungi (Eumycetoma) or by aerobic actinomycetales (Actinomycetoma). In order of frequency, the etiologic agents of the actinomycetoma are:

*Actinomadura madurae*, *Nocardia brasiliensis*, *Streptomyces somaliensis*, *N. asteroides*, *N. otitidis caviarum*, (*N. caviae*), *A. pelletieri*, *S. paraguayensis* and *Nocardia dassonvillei*<sup>2, 8, 50</sup>.

Actinomycetoma usually begins at the site of a minor localized injury, most frequently induced by a thorn or a splinter soil contaminated.

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As a consequence, the disease is more commonly localized on the feet. The traumatic inoculation of the organisms into the skin often causes primary cutaneous or subcutaneous infections, which clinically are recognized as the "Mycetoma Syndrome". The characteristics of this syndrome are the presence of oedema, sinus tracts and granules<sup>8, 9, 22, 32, 38, 54</sup>.

Minimycetomas, as well as chancriform lesions involvement of the regional lymph nodes, with a clinical picture similar to sporotrichosis<sup>3, 6, 18, 23, 29, 30, 34, 35, 43, 48</sup> has been reported in the infection by *N. brasiliensis*.

In Venezuela, Actinomycetoma is the most frequently recognized form of disease caused by the aerobic actinomycetes<sup>3, 5, 12, 17, 19, 21, 24, 33, 36, 41, 44, 47, 51, 55, 56, 58, 59</sup>. There is a noticeable lack of epidemiological studies to ascertain the incidence of diseases caused by these microorganisms. CAMPINS<sup>13, 17</sup>, CONVIT et al<sup>19</sup>, ALBORNOZ,<sup>9</sup> and SERRANO et al<sup>51</sup> have reported isolated cases of Actinomycetoma infections through different Venezuelan areas.

The present paper is a review of cases of Actinomycetoma in Venezuela during a ten year period (1976-1986). All cases were reviewed and studied in his clinical, histological and microbiological aspects.

## MATERIAL AND METHODS

The data related to the present paper were obtained as follows: 1) Personal interview and clinical examinations of patients. 2) Analysis of medical records of mycetoma patients. 3) Personal interviews with Dra. María Cecilia de Albornoz from the Biomedicine Institute, Caracas; Dr. Dante Borelli and Dra. Carmen Marcano from the Institute of Tropical Medicine "Universidad Central de Venezuela", Caracas; Dr. Gregorio Volcan, "Universidad de Oriente" School of Medicine, Ciudad Bolívar State, Dr. Hernán Vargas, Dra. Nieves Vargas de Caminos and Lic. Luz Mila Meza, School of Medicine, "Universidad del Zulia" Maracaibo, Venezuela. Lic. Cristina Pérez "Universidad de Carabobo" La Morita, Maracay, Aragua State; Dr. E. Sawertein "Hospital General Luiz Razetti" Barinas, Barinas State and Lic. Francisco Yegres "Universidad Experimental

Francisco Miranda", Coro, Falcón State. All of the above mentioned persons provided information on cases that they had observed as well as on sources of biopsy samples and of some of the microbiologically studied strains.

The diagnosis of actinomycetoma of the cases studied, were based on: a) Clinical and epidemiological features. b) Histological examinations (H & E) stain of biopsy samples. c) Microbiological examination of 30 cultures that were isolated from mycetoma patients. The microbiological studies were performed according the following methodology. 1) Morphological studies of the culture growth in Brain Heart Infusion (BHI). The Gram and Kinyou methods were used as staining procedures. The physiological and biochemical properties, such as decomposition and proteolytic activities, utilization of nitrogenous compounds, sensitivity to Lysozyme and utilization of sugars, were studied as recommended by GOODFELLOW et al<sup>25, 26</sup> GORDON & MIHM<sup>27, 28</sup> and BERD<sup>10</sup>.

The whole cell chemotype, as well as the lipids, were evaluated according MORDARSKA et al<sup>37</sup> and LECHEVALIER & LECHEVALIER<sup>39,40</sup>. The final diagnosis and classification of the study strain was based on GOODFELLOW & CROSS<sup>24</sup>.

## RESULTS

In Venezuela, Actinomycetoma has been the most frequently recognized form of disease caused by the organisms that produce Mycetoma (See Table 1). All the cases studied were the results of observations and diagnosis made during a 10 year period (1976-1986). A total of 47 cases were recorded. Table 2 shows the distribution by States of Venezuela of the studied cases and its etiological agents. Out of the 47 cases (see Table 3) twenty cases were caused by *A. madurae* (12 cases were microbiologically confirmed and 8 by histological diagnosis). *N. brasiliensis*, was reported in 13 cases, all microbiologically confirmed. *Nocardia spp.* was observed in 7 cases (diagnosis based on "small granule", H & E observations) *S. somaliensis*, 4 cases (2 cases were microbiologically confirmed and 2 cases through histology). *N. asteroides* in 2 cases microbiologically confirmed and *N. otitidis ca-*

**vium** in 1 case. In Table 4 are shown the results of the physiological, biochemical and chemotaxonomic studies of thirty of the culture proven cases of Actinomycetoma.

TABLE 1  
Reported cases of actinomycetoma in Venezuela, until 1986

Author(s)	Reference	Year	State	Number of cases	Etiblogic Agent	Diagnosis by	
						Histology	Culture
Rangel	45, 46	1909	Federal	1	<i>A. madurae</i>	+	— **
			Zulia				
Cuenca	20, 21	1927	Distrit.	1	<i>N. brasiliensis</i>	+	+
Briceño & Villalobos	12	1927	Lara	1	<i>N. brasiliensis</i>	+	+
O'Daly	44	1938	Aragua	1	<i>A. madurae</i>	+	+
Montemayor	36	1950	— —	1	<i>N. asteroides</i>	+	+
Velutini	56	1951	Lara	1	<i>N. asteroides</i>	+	+
Salas & Borelli	47	1955	— —	1	<i>N. brasiliensis</i>	+	+
Campins	13, 15	1955	Lara and Yaracuy	4	<i>N. brasiliensis</i>	+	+
				3	<i>A. madurae</i>	+	+
				4	unknow	+	—
Alarcón et al.	3	1956	Miranda	1	<i>N. brasiliensis</i>	+	+
Barnola et al.	7	1956	Lara	1	<i>N. brasiliensis</i>	+	+
Montemayor	33	1958	— —	1	<i>N. brasiliensis</i>	+	+
Rincón, F. G. et al.	44	1961	Zulia	1	<i>S. pelletieri</i>	+	+
Convit et al	19	1961	Lara	9	<i>N. brasiliensis</i>	+	+
(review cases)			Zulia				
			Miranda				
			Federal				
			Distrit.	7	<i>A. madurae</i>	+	+
Borelli, & Leal	11	1969	Andean	1	<i>N. brasiliensis</i>	+	+
			región				
Vargas	55	1973	Zulia	1	<i>S. somaliensis</i>	+	+
Zamora et al.	59	1974	Lara	1	<i>N. brasiliensis</i>	+	+
Albornoz et al.	4	1977	Miranda	1	<i>A. madurae</i>	+	+
Volcan	58	1978	Bolívar	1	<i>N. brasiliensis</i>	+	+
Albornoz	5	1978	Anzoátegui	1	<i>Nocardia</i> spp	+	+
(review cases)			Aragua				
			Falcón, Guárico	19	<i>N. brasiliensis</i>	+	+
			Lara, Miranda	9	<i>A. madurae</i>	+	+
			Sucre, Zulia	3	<i>N. asteroides</i>	+	+
				3	<i>S. somaliensis</i>	+	+
				1	<i>A. pelletieri</i>	+	+
				2	<i>Nocardia</i> spp	+	+
Serrano et al	51	1985	Lara & Falcón	10	<i>A. madurae</i>	+(8)***	+(2)***
				5	<i>N. brasiliensis</i>	+	+
				2	<i>N. asteroides</i>	+	+
				1	<i>N. caviae (otitidis caviarum)</i>	+	+
				13	<i>Nocardia</i> spp	+	—
				4	<i>S. somaliensis</i>	+(2)***	— (2)***

\* means: diagnosis made by microscopic observation of the grain.

\*\* means: no culture obtained.

\*\*\* Cases.

The histological studies reveal that in the Actinomycetoma caused by Nocardiae, the H & E stain shows the presence of small deep blue oval or round grains. These grains have a peripheral zone composed mainly of filamentous cells, which often present a club shape and a central

zone partially stained in blue or red colour where short type bacillar and coccoidal forms were observed. The tissue reaction pattern in these cases were that of a microabscess surrounded by granulation tissue. These kind of granules and tissue reaction pattern was observed in 23 of the stu-

TABLE 2  
THE DISTRIBUTION OF ACTINOMYCETOMA  
IN DIFFERENT STATES OF VENEZUELA  
(1976-1986)

STATES	ORGANISM						TOTAL
	<i>A. MAD</i>	<i>N. BRAS</i>	<i>N. AST</i>	<i>N. CAV</i>	<i>N. SPP</i>	<i>S. SOM</i>	
ARAGUA	2						2
BARINAS		1					1
FALCON	2	2			2		6
FED. DIST.	2	2			1		5
LARA	8	5	2	1	4	4	24
MIRANDA	3	2					5
YARACUAY	1	1					2
ZULIA	2						2
TOTAL	20	13	2	1	7	4	47

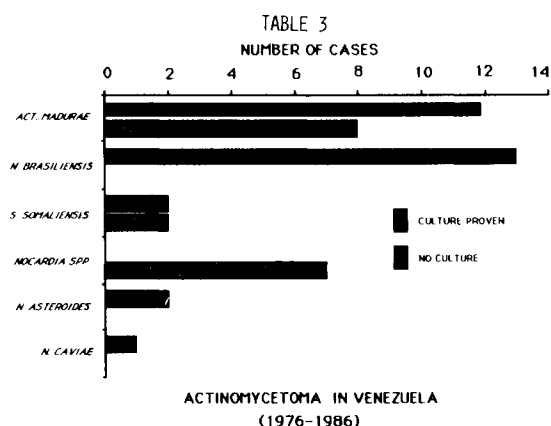


TABLE 4  
Physiological and chemotaxonomic characteristics of 30 strains, isolate from actinomycetoma cases in Venezuela<sup>1</sup>

TEST	<i>A. Madurae</i> (12 strains)	<i>N. asteroides</i> (2 strains)	<i>N. brasiliensis</i> (13 strains)	<i>N. otitidis caviarum</i> (1 strain)	<i>S. somaliensis</i> (2 strains)
Gram	+	+	+	+	+
Acid fastness	---	± <sup>2</sup>	±	±	---
Hydrolysis and Descomposition					
Casein	+	---	+	---	+
Hypoxanthine	+	---	+	+	---
Starch	+	+	+ <sup>3</sup>	+	+
Tyrosine	+	---	+	---	+
Urea	---	+	+	+	---
Xanthine	---	---	---	+	---
Acid. Production from					
Cellulose	+	---	---	---	---
l inositol	+ <sup>4</sup>	---	+	+	---
d mannitol	+	---	+	+	---
Xylose	+	---	---	---	---
Resistance to Lysozyme	---	+	+	+	---
Nitrite from nitrate	+	+	+	+	---
Whole organism hydrolysate analysis					
DL — DAP	+	+	+	+	---
LL — DAP	---	---	---	---	+
Micolic Acid thin layer spot.	---	+	+	+	---

1 Table shows most significant results

2 a weak reaction was observed

3 6 strains were negative

4 4 strains were negative

died cases. The histological observations of the *A. madurae* cases (20 cases) present a typically multilobed or vermin-shaped grain with a peripheral deep blue band and a colorless or faint

blue center. The tissue reaction pattern is that of a non specific inflammatory reaction with microabscess formation surrounded by macrophages with a foamy cytoplasm, resulting in a lesion

that has the appearance of an "histiocytic granuloma".

The lesions produced by *S. somaliensis* (4 cases) show a typical granulomatous tissue reaction, composed of epithelioid and giant cells that surrounded the parasitic grain. Fibrosis is observed around the periphery of the lesions. The granules are round or oval compact. They are composed of a matrix of amorphous material showing some artificially produced slits. The matrix may show some affinity for eosin at the periphery but no clubs shapes were observed. In the present report *A. madurae* was found to be the most frequent agent of mycetoma (20 cases), followed by *N. brasiliensis* (13 cases). The majority of the studied patients were 30 to 59 years old. As reported in previous studies, we observed that the most frequent location of the mycetoma was on the foot (30 cases), followed by the leg (6 cases). Most of the patients (80%) were peasants and men were more commonly affected (35 cases, 74.5%) than women (12 cases, 25.5%).

#### DISCUSSION

There have been no detailed studies attempting to determine the extent or epidemiology of Actinomycetoma throughout Venezuela. The present paper is based on cases reported in the literature and on personal communications with dermatologists at some of the key hospitals, (21 cases). The data for the remaining 26 cases were obtained by personal interview with the patients. Currently it is not possible to state prevalence of the disease in Venezuela. In the Venezuelan literature on mycetoma one can find about 96 actinomycetoma cases reported in the whole country (Table 1). By studying histologic sections of biopsy samples from 30 culture proven cases, as other investigators have previously reported<sup>22, 38, 51, 57</sup>, we were able to identify causal agent with a 100% correlation with the microbiological results.

The importance of histological examination of actinomycetomas, as shown in the present study, is evident by the fact that the causal agent of the actinomycetoma could be recognized in 40 of 47 cases by histology alone. There is no doubt that histological diagnosis has limitations since in the present report 7 cases could be diag-

nosed only as *Nocardia* spp since no culture was possible. However the clinical, and radiological examination and the response to the treatment confirmed the presumptive diagnosis. In these studies the histological diagnosis was based upon the size and shape of the granules as well as in the characteristic of the cellular and tissue reaction pattern. It is important to emphasize that the histological examination should be supplemented by simultaneous culture either of biopsy tissues or granules when obtained.

In Venezuela actinomycetomas are observed more commonly than eumycetomas<sup>5, 15, 19, 51, 52</sup>. According to current reports *A. madurae* is the most frequent etiologic agent of actinomycetoma in Venezuela. Similar results have been reported in India by PANKAJALAKSHMI et al<sup>12</sup> and in the United States by TIGHT et al<sup>33</sup> LA-CAZ<sup>31</sup>, and LAVALLE<sup>32</sup> indicated that *N. brasiliensis* is the most common etiologic agent of actinomycetoma in Brazil and México respectively. Most of the reported cases involve individuals living and working in the rural areas and the majority of these infections are in males, which outnumber females by a 4:1 ratio. The patients ages ranged from 18 to 80 years, and their occupation is usually either field laborers, herdsmen or peasants. Only 3 cases of Actinomycetoma were diagnosed in persons residing and working within urban areas; two of these were caused by *A. madurae* and 1 case caused by *N. brasiliensis*. Most of the clinical cases were observed after the disease was well established within the host, and the individuals sought medical attention only after the disease had progressed to the stage of being debilitating. Venezuela has many rural communities and some of them are far away from the large metropolitan hospitals. Most of the inhabitants of these rural areas have a low income and belong to lower socioeconomic group. Because of these factors it is difficult to make an early diagnosis of infections caused by these actinomycetes, thus resulting in a potentially serious problem. Actinomycete infections that are recognized early frequently respond to therapy, whereas those infections that have been allowed to progress are not prone to successful treatment. It is interesting to note that according to CONTI-DIAZ<sup>18</sup> mycetomas in Uruguay are usually diagnosed early. This is due to prompt medical consultation, the absence of

significant geographical obstacles and the existence of an adequate health education program. In other countries, such as Venezuela, Brazil, India, Mexico or Sudan<sup>1, 31, 32, 42, 51, 52</sup>, the existence of numerous geographical barriers, vast territories and inadequate health education of the population discourage patients with this not painful disease from seeking prompt medical advice. The provision of information about mycetomas to physicians, medical students, nurses and paramedicals working in countries where mycetomas are endemic is also important.

### RESUMO

#### Aspectos histológicos e microbiológicos de casos de actinomicetoma na Venezuela.

Os autores, em um período de 10 anos (1976-1986) realizaram um estudo clínico, histopatológico e micológico em 47 casos de actinomicetoma. Os agentes etiológicos isolados foram: *Actinomadura madurae* — 20 casos (42,5%); *Nocardia brasiliensis* — 13 casos (27,6%); *Nocardia* spp. — 7 casos (14,8%); *Streptomyces somaliensis* — 4 casos (8,5%); *Nocardia asteroides* — 2 casos (4,2%) e *N. otitidis caviarum* (*N. caviae*) — 1 caso (2,1%). A maioria dos casos procedia de zona rural, prevalecendo a infecção no sexo masculino (4/1). A idade dos pacientes variou de 18 a 80 anos. Dos 47 casos registrados, 24 foram observados no Estado de Lara, representando 51% do total das observações.

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